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Plant-derived triterpenoids and analogues as antitumor and anti-HIV agents†

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Abstract

This article reviews the antitumor and anti-HIV activities of naturally occurring triterpenoids, including the lupane, ursane, oleanane, lanostane, dammarane, and miscellaneous scaffolds. Structure–activity relationships of selected natural compounds and their synthetic derivatives are also discussed.

1 Introduction

Natural products are an excellent reservoir of biologically active compounds. For centuries, extracts from natural products have been a main source of folk medicines, and even today, many cultures still employ them directly for medicinal purposes. Among the classes of identified natural products, triterpenoids, one of the largest families, have been studied intensively for their diverse structures and variety of biological activities. As a continued study of naturally occurring drug candidates, this review describes the research progress over the last three years (2006–2008) on triterpenoids possessing cytotoxic or anti-HIV activity, with focus on the occurrence, biological activities, and structure–activity relationships of selected compounds and their synthetic derivatives.

2 Potential antitumor effects of triterpenoids

2.1 The lupane group

Betulinic acid (**1**) is a naturally occurring pentacyclic triterpene belonging to the lupane family. It is present in many terrestrial plant species, e.g., *Ancistrocladus heyneanus*, *Diospyros leucomelas*, *Syzygium formosanum*, *Tetracera boliviana*, *Tryphyllum peltatum*, and *Ziziphus* vulgaris.[1–3] Compound 1 can also be obtained in quantity from the bark of the London plane tree, *Platanus acerifolia*.[4,5] Table 1 lists other plant sources of **1** reported since 2006.

Trumbull and co-workers[6] identified the inhibitory activities of compound **1** against tumor promotion in 1976. Later, its action was identified as a melanoma-specific cytotoxicity mediated by the induction of apoptosis.[7] The cytotoxicity as well as mechanism of action of 1 have been reviewed.[8–11] Although it was initially identified as a melanoma-specific cytotoxic agent, in more recent studies, 1 showed antiproliferative activity against MCF-7 cells (GI_{50}: 0.27 μM),[12] as well as neuroblastoma (SKNAS), rhabdomyosarcoma-medulloblastoma (TE671), breast carcinoma (T47D), lung carcinoma (A549), colon

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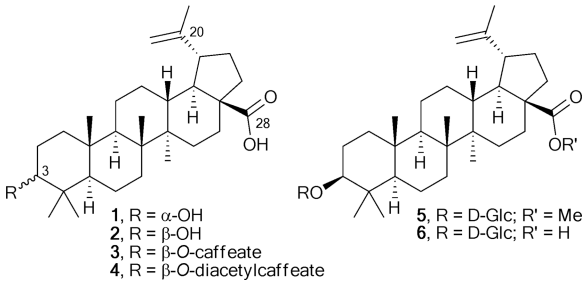
adenocarcinoma (HT-29), multiple myeloma (RPMI8226), cervical carcinoma (HPCC), and glioblastoma multiforme (HPGBM) cell lines (IC_{50}: 2.4–4.5 μM).[13] It also showed broad-spectrum cytotoxicity towards lung, colorectal, breast, prostate, and cervical cancer cell lines,[14] as well as drug-resistant colon adenocarcinoma cell lines (SNU-C5/WT, SNU-C5/5FU-R, and SNU-C5/OXT-R).[15]



Compound **1** induces apoptosis[11,16] through the mitochondrial pathway.[15,17,18] A typical decrease in *bcl-2* and *cyclin D1* gene expression and increase in *bax* gene expression was observed in several cancer cell lines treated with **1**,[13,19] which agreed with prior literature.[18] Subsequent studies on its anticancer mechanism revealed that **1** is a potent activator of the chymotrypsin-like activity of the proteasome.[20] In addition, **1** decreases expression of vascular endothelial growth factor (VEGF) and the antiapoptotic protein survivin in prostate cancer cells (LNCaP) by activating selective proteasome-dependent degradation of the transcription factor's specificity proteins.[21] Compound 1 also inhibits NF-κB expression in androgen-refractory human prostate cancer cells (PC-3), which exhibit high constitutive NF-κB expression.[19]

Furthermore, although **1** reportedly is an inhibitor of human topoisomerases (topo) **I** and IIα,[22,23] it does not show synergistic effects with other topo-I inhibitors. In contrast, **1** inhibited the formation of topo-I DNA cleavable complexes (apoptotic mediatora) induced by camptothecin, staurosporine, and etoposide in prostate cancer cells.[24] This study also indicated that the tumor death mediated by **1** can be counteracted by the mitogen-activated protein kinase 1 (MAPK1) inhibitor U0126 in melanoma cells.[25]

Structure–activity relationship (SAR) studies of **1** have led to the preparation of numerous C-3 hydroxyl, C-20 double bond, C-28 carboxylic acid, and miscellaneous modified analogues. In most cases, C-3 modification led to altered cytotoxic potency and selectivity, while reduction of the C-20–C-29 double bond and replacement of the C-28 carboxyl group with ester and amide side chains generally gave derivatives inactive against cancer cell lines.[9] Recent approaches revealed similar results. Compound **2**, the C-3 epimer of **1**, demonstrated decreased cytotoxicity when compared with **1**.[56] Betulinic C-3 esters **3** and **4** exhibited better activity against KB cells.[57] 3-*O*-Glycosidated derivatives **5** and **6** were 8- to 12-fold more potent than **1** (IC_{50}: 2.6–3.9 μM) against cancer cells and showed better selectivity compared with healthy cells (IC_{50}: 31 μM).[58] The C-28 monosaccharide derivatives (**7**) showed slightly increased cytotoxicity, whereas trisaccharide analogues (**8**) were inactive.[59] In anti-HIV studies, adding a C-28 side chain was a successful structure modification strategy; however, the resulting potent anti-HIV lead **9** (IC9564) lost the ability to activate chymotrypsin-proteasomal activity compared with **1**.[20]

2-Cyano-3,12-dioxooleana-1,9(11)-dien-28-oic acid (CDDO) is a promising anticancer synthetic oleanolic acid analogue (see Section 2.2), and this same CDDO modification concept (incorporating a 2-substituted-1-en-3-one A-ring in the triterpenoid skeleton) was also applied to **1**. The resulting A-ring-modified 2-substituted-1-en-3-one derivatives (**10**–

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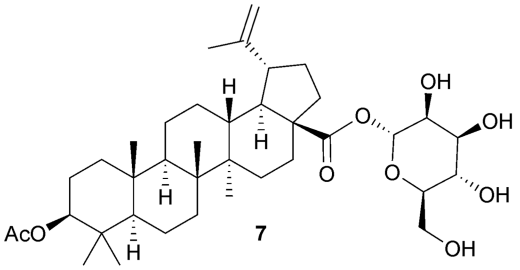
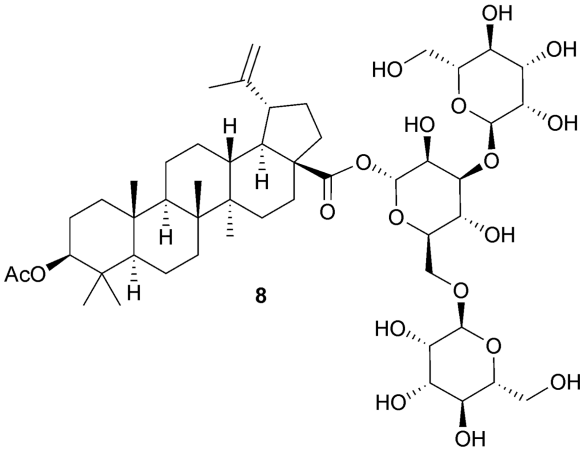
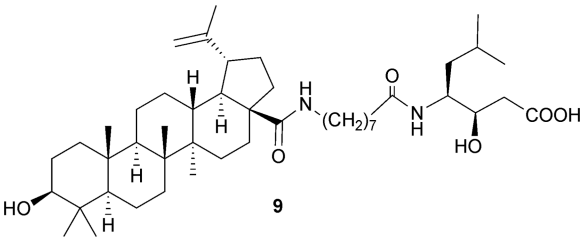
14) showed enhanced cytotoxic or cytostatic activity against pancreatic (Panc-28), colon (SW480), leukemia (U937), and myeloma (RPMI 8226) cancer cell lines.[60,61] Compared with **10**–**12**, analogues **13** and **14**, which have a methylcarboxy rather than cyano group at C-2, showed increased potency in an apoptosis assay.[61] Expanding the ring system by incorporating an indole or pyrazine ring at C-2 and C-3 afforded heterocyclic analogues (**15**–**19**), which were more potent than the parent compound, **1**, against pancreatic (MIAPaCa2), ovarian (PA-1), and other (SW620, A549, HT-29, K-562, K-562-tax, and -b2–4) cancer cell lines.[62,63] Non-typical synthetic approaches to C-30 and E-ring modifications led to the oxo-lupane analogues 20–23, which also showed enhanced cytotoxicity against CEM cells (IC_{50}: 5–7 μM).[64]







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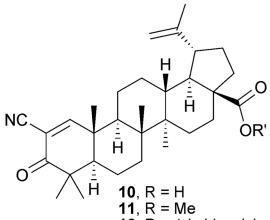

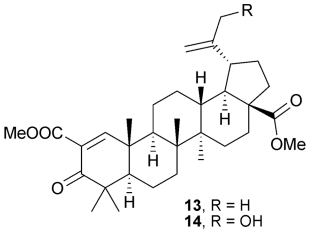

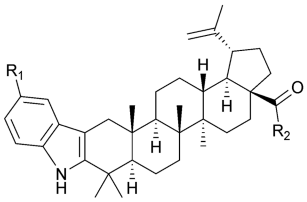

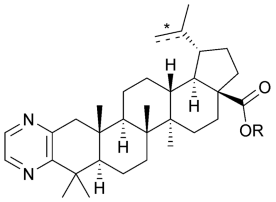

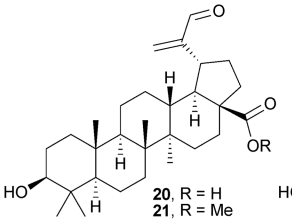

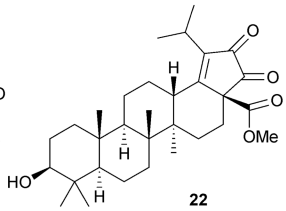

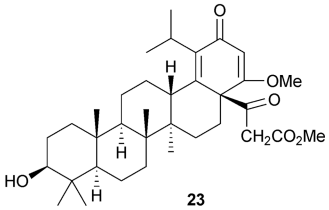

Compound **1** has also been evaluated for additional biological activities. It reduces the activity of cholesterol acyltransferase (ACAT-1 and ACAT-2)[48] and the formation of triglyceride (TG) by inhibiting diacylglycerol acyltransferase in human HepG2 cells.[31] When studied for cardiovascular activity, **1** demonstrated up-regulation of eNOS and down-regulation of NADPHoxidase in human endothelial cells.[65] The proinflammatory effect of **1** was proved by blocking the interaction of C1q with antibodies in the classical pathway.[66] Moreover, **1** displayed anti-inflammatory activity through the suppression of both NO and PGE2 generation by macrophages, with IC_{50} values of 0.7 and 0.6 μM, respectively.[67] Compound **1** is also a competitive inhibitor of the protease (3CL) of SARS-CoV, a highly virulent coronavirus, with a K_i value of 8.2 μM.[68] In other experiments, **1** and various C-3 modified analogues showed antimicrobial activity, with inhibitory effects toward *Mycobacterium tuberculosis* (MIC: 10–109 μM),[30,69] *Trichophyton soudanense* (MIC: 54.8 μM), and *T. mentagrophytes* (MIC: 27.4 μM).[70] Compound **1** also inhibited the invasion of *Porphyromomas falciparum* into erythrocytes, with IC_{50} values of 13.8 μM,[71] and blocked the binding effects of heat-labile entero-toxin (LT) of *E. coli* in intestinal epithelial cells, resulting in the suppression of LT-induced diarrhea.[72]

Lupeol (**24**), a very common lupane-triterpene widely distributed in the plant kingdom, occurs across a multitude of taxonomically diverse genera and geographical areas. In a

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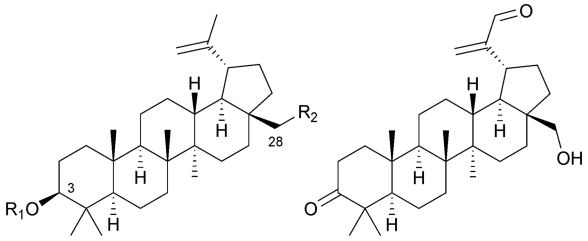
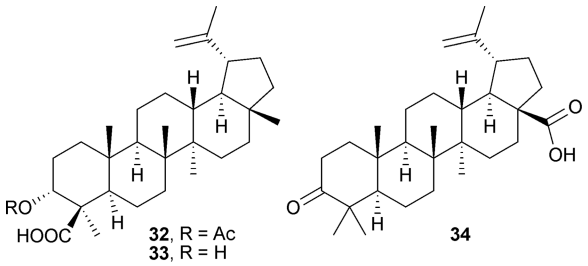
survey of the Chemical Abstracts database, more than 100 literature references during the period 2006 to 2008 reported the occurrence of lupeol. A recently published review described the chemopreventive prospects, molecular target, and mechanism of action of **24**.[73] In an earlier investigation of apoptotic induction and cell arrest in various cancer cells, further molecular-level phenomena involving MAPK, PI3K/Akt, death receptor, and NF-κB signaling pathways were also revealed.[73] The following *in vitro* and *in vivo* studies showed similar results; **24** inhibited the growth of LNCaP cells (IC_{50}: 75 μM) and significantly reduced testosterone-induced prostate changes in mice by a factor of 1.4.[74] Compound **24** arrested the cell cycle at the G(1)-S phase in PC-3 cells[75] or the G2/M phase in 451Lu cells and 451Lu xenografts in nude mice.[76] In addition, **24** caused induction of capase-3, and elevation of the Bcl-2/Bax ratio in LNCaP, PC-3 and 451Lu cells were observed, which are characteristics of mitochondria-mediated apoptosis.[74–76] Interestingly, pre-treatment or post-treatment with **24** at a dose of 200 mg/mouse showed 56% and 43% preventive effects, respectively, against DMBA-induced DNA breakage.[77]



24, $R_1 = R_2 = H$
25, $R_1 = H$; $R_2 = OH$
26, $R_1 = \alpha$-D-Man; $R_2 = H$
27, $R_1 = H$; $R_2 = \alpha$-D-Man
28, $R_1 = \beta$-(Glc or Rha or Ara); $R_2 = H$
29, $R_1 = H$; $R_2 = \beta$-(Glc or Rha or Ara)
30, $R_1 = \beta$-Glc; $R_2 = H$

Betulin (**25**), a C-28 hydroxylated lupane commonly isolated together with **1**, generally showed lower activity in cytotoxic assays than **1**.[12,59,62,78,79] However, exceptions were found against A-549, B16-F1, DLD-1, and WS1 cell lines.[58] In an SAR study of glycoside derivatives, glycosidation at C-3 or C-28 of **25** gave **26** and **27**, which showed slightly enhanced cytotoxic activity.[59] In other literature reports, derivatives **28** and **29** with C-3 or C-28 monosaccharide units, respectively, lost cytotoxicity.[58] In contrast, the 3-O-glycosylated derivative of lupeol (**30**) showed 7–12-fold improved cytotoxicity.[58]

28-Hydroxy-3-oxo-lup-20(29)-en-30-al (**31**), obtained from the stems of *Microtropis fokienensis* and *Perrottetia arisanensis*, showed cytotoxic effects toward Hep3B, MCF7, Ca9–22, and HL60 cell lines (IC_{50}: 1.4–4.7 μM).[56] The acetyl ester **32** isolated from *Boswellia carteri* was cytotoxic against IMR-32 (IC_{50}: 4.1 μM) and SK-N-SH (IC_{50}: 4.7 μM) cell lines, while its free acid analogue 33 was less potent (IC_{50}: >30.9 μM).[80] Betulonic acid (34) from *Betula platyphylla* showed cytotoxic effects against KB (IC_{50}: 2.3 μM) and KB-C2 (IC_{50}: 3.8 μM) cell lines.[81]



32, R = Ac
33, R = H

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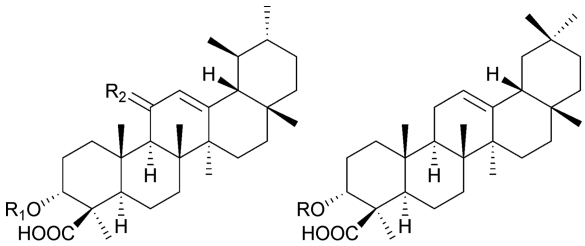
2.2 The ursane and oleanane groups

The gum resin of genus *Boswellia* (olibanum or frankincense) has been used traditionally in Asia and Africa as a folk medicine for the treatment of arthritis and inflammatory disorders.[82] The main active components of the resin are boswellic acids (BAs, **35**–**40**), which are pentacyclic triterpene carboxylic acids isolated from various *Boswellia* species (Burseraceae), including B. carterii, B. *frereana*, B. *papyrifera*, *B. sacra*, and *B. serrata*.[83,84] Chemically, BAs can differ in the positions of the two methyl groups on ring-E; β-BAs (**35**–**38**) have 19,20-dimethyl substitution, while α-BAs (**39**–**40**) have 20,20-dimethyl substitution, classified as the ursane and oleanane groups of triterpenes, respectively.



35, R_1 = H; R_2 = H,H
36, R_1 = Ac; R_2 = H,H
37, R_1 = H; R_2 = O
38, R_1 = Ac; R_2 = O

39, R = H
40, R = Ac

The relative potency of BAs, proposed mechanisms of action, and molecular targets, including non-redox-type 5-lipoxygenase (5-LOX), platelet 12-lipoxygenase (p12-LO), human leukocytes elastase (HLE), cytochrome P450 enzymes (CYP 2C8/2C9/3A4), topoisomerases I and IIa, and NF-κB kinase (IKK α/b), have been reviewed.[83,85] An inhibitory effect on cycloxygenase-1 (COX-1) by **38** was also identified.[86] These targets are indicative of the anti-inflammatory (5-LOX, p12-LO, HLE, and COX-1) and anticancer (topo I/IIa and IKK α/β) activities of the BAs.

Fig. 1 summarizes the signal transduction scheme of **38**-induced apoptosis. Although the effector caspases and other markers have been identified, the primary molecular targets as well as the precise role of mitochondria are still unclear. For details, see the review by Poeckel *et al*.[83]

Compound **38**, which is commonly known as AKBA (3-*O*-acetyl-11-keto-β-boswellic acid), has been the most well explored BA. A recent discovery revealed that **38** showed moderate to low toxicity against human skin-derived normal cell lines.[87] However, **38** induced apoptosis in PC-3 and LNCaP cells through a death receptor (DR-5)-mediated pathway, which is a signal transduction cascade involving the activation of capase-8 and capase-3 in apoptosis.[88] The inhibitory effect of **38** was significant in comparison with those of indomethacin and cyclophosphamide against bFGF-induced angiogenesis using an *in vivo* matrigel plug assay.[89] Two C-3 acetylated BA derivatives, **36** and **40**, showed almost comparable activity with cisplatin against neuroblastoma (NB-39 and SK-N-SH) cell lines.[80] Compound **40** triggered apoptosis by activation of caspase-3 and induction of DNA fragmentation in PC-3 cells and PC-3 xenotransplants in chick chorioallantoic membrane.[90] Compound **36** showed similar inhibitory effects to those of β-carotene, reported as 380 and 397 molar ratios, respectively, to 32 pM TPA used as inhibitor, in the TPA-mediated EBV-EA activation assay.[80] In several anti-inflammatory studies, treatment with BAs from *B. serrata* diminished chemical- or stress-induced edema, arthritis, and gastric ulcer, with moderate to low activity.[91,92] Compound **38** demonstrated a synergistic effect in combination with indomethacin on kainic acid-induced excitotoxicity and oxidative damage *in vitro*,[87,93] and with glucosamine for the treatment of murine edema and arthritis.[94]

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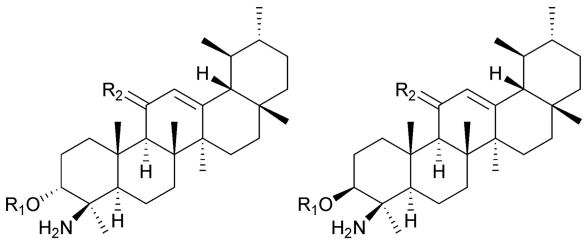
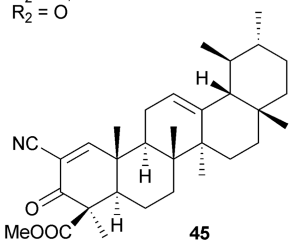
In anti-inflammatory and other assays, β-BAs generally show greater potency than α-BAs. In contrast, 3-*O*-acetyl-α-boswellic acid (AαBA, **40**) was the most potent analogue (IC_{50}: 1–3 μM) compared with β-derivatives against purified topo I.[83] The cytotoxic SAR of BAs has seldom been addressed, but in recent studies, **40** showed higher cytotoxic activity than **39**, indicating the importance of a C-3 acetyl group for optimal potency of α-BAs.[80] Furthermore, 4-amino β-BA analogues (**41**–**43**) displayed enhanced cytotoxicity compared with the corresponding β-BAs possessing a 4-carboxylic acid, while C-3 β-epimers of these amino analogues (**44**) did not show improved activity.[95] A CDDO-like (see Section 2.2) analogue (**45**) showed enhanced activity against A-549, A-431, HL-60, MCF-7, T47D, and HT1080 cell lines, with sub-micromolar EC_{50} values (EC_{50}: 0.10–0.59 μM).[96]



41, R_1 = Ac; R_2 = H,H
42, R_1 = H; R_2 = H,H
43, R_1 = H; R_2 = O

44, R_1 = ester; R_2 = H_2 or O



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Ursolic acid (3β-hydroxy-urs-12-en-28-oic acid (**46**) is a prevalent pentacyclic triterpenoid carboxylic acid. It has been found in various plants in both aglycone and glycoside forms, and traditional uses of plants containing **46** in folk medicine are abundant. Modern studies have shown that **46** possesses many biological activities, such as anti-oxidative, anti-inflammatory, antitumor, and hepato-protective activity. The diverse inflammatory effects of **46** were reviewed by Ikeda *et al.* in 2008.[97] This review also summarized the inhibitory activity of **46** on cancer cells, which may be due to suppression of inhibitors of the NF-κB pathway and p65 phosphorylation, thereby causing down-regulation of the expression of downstream oncogenes. Compound **46** may also reduce skin tumor formation by inhibiting the binding of carcinogen to epidermal DNA or cell membrane. Furthermore, **46** induces cell differentiation and apoptosis in certain cancer cell lines. For details, see the review by Ikeda *et al.*[97]

Current work has provided more evidence on the bioactivity of **46**. Inhibitory effects were observed on both the PI3K-Akt and MAPK P44/42 pathways, which are associated with cell apoptosis in endometrial cancer cell lines (SNG-II and HEC108).[98] Compound **46** exhibited chemopreventive effects during the cancer initiation phase of an *in vivo* inhibitory assay of aberrant crypt foci (ACF), which are putative precursors of colon cancer, and increased neutral sphingomyelinase (N-SMase) activity.[99] Compound **46** also inhibited endogenous reverse transcriptase (RT), an enzyme involved in the control of cell proliferation and differentiation, in melanoma (A375) and anaplastic carcinoma (ARO) cell lines. Down-regulation of the expression of two cancer-related genes, *c-myc* and *cyclin-D1*, in A375 and/or ARO cells was stimulated by **46**.[100] In contrast, **46** reduced the amount of L1210 cell growth inhibition induced by doxorubicin. The result might be due to scavenging of ROS

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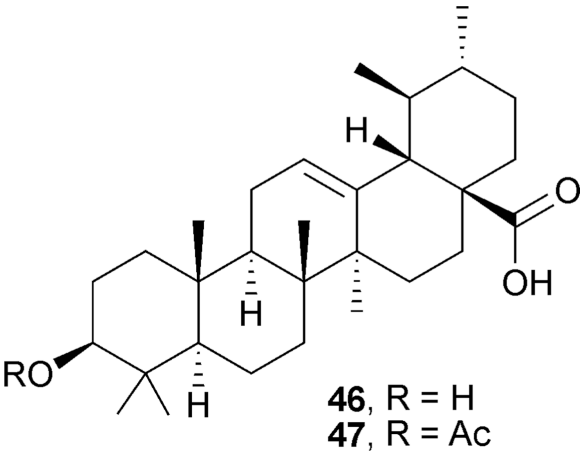
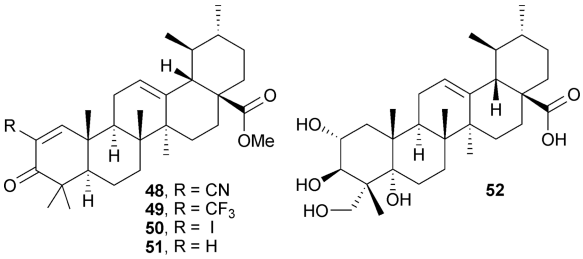
involved in the apoptotic processes induced by doxorubicin.[101] A similar inhibitory pattern was observed on H_2O_2-induced DNA breakage in HL-60 cell lines treated with **46**.[102]



In other SAR studies, compounds with an acetyl moiety on the C-3 hydroxy group (**47**) showed greater potency than those with a free hydroxyl.[103] In addition, the CDDO modification strategy was applied. The C-2 cyano or trifluoromethyl derivatives of 1-en-3-one-ursolic acid (**48** and **49**) showed better activity than C-2 iodo- and non-substituted analogues (**50** and **51**) in anti-proliferation assays using KU7, 253JB-V, Panc-1, and Panc-28 cancer cell lines (IC_{50}: 0.17–1.13 μM).[104]



The bioactivities of other naturally occurring ursane-triterpenes have also been reported. Topical application of asiatic acid (**52**) resulted in a significant reduction in skin tumor formation induced by TPA, and TPA-induced [^{3}H]thymidine incorporation was lessened. Concurrently, **52** inhibited the TPA-induced generation of NO and expression of iNOS and COX-2, which are important factors in tumor promotion.[105] In addition, **52** induced apoptosis in PPC-1 and U-87MG cancer cells. The apoptotic phenomena included early activation of caspase-2, −3, and −8 in PPC-1 cells[111] and caspase-9 and −3 in U-87MG cells.[112] Intracellular release of Ca^{2+} was observed in both cell lines, and U-87MG cell death was alleviated by BAPTA/AM, an intracellular Ca^{2+} inhibitor. These results implied that the cell death is attributable to Ca^{2+}-mediated necrotic apoptosis.[106]

Two new ursane-type triterpenes, microfokienoxane C (**53**) and 3β,28-dihydroxy-11α-methoxyurs-12-ene (**54**), were isolated from the leaves of *Microtropis fokienensis*. Compound **53** was cytotoxic against HepG2 and Hep3B cancer cell lines, with IC_{50} values of 8.1 and 9.5 μM, respectively. Compound **54** showed activity against the HepG2 cell line, with an IC_{50} value of 9.2 μM.[107]

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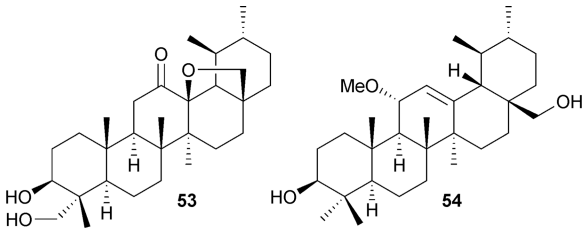
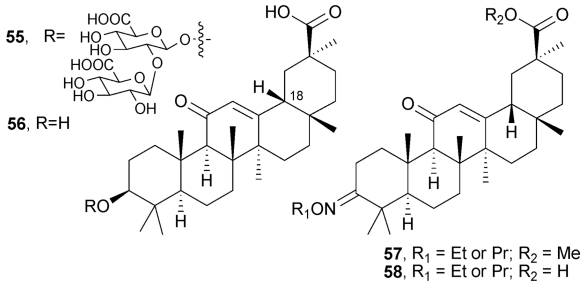
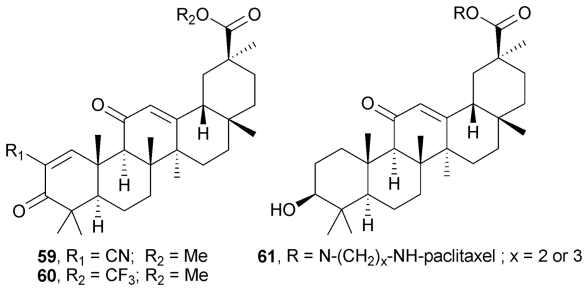


Glycyrrhizin (**55**) and its aglycone, glycyrrhetic acid (**56**, GA), are abundant constituents of licorice (most familiarly the species *Glycyrrhiza glabra*). The aglycone **56** exists as 18α- and 18b-isomers, and 18b-GA was more effective than 18α-GA in inhibiting the mutagenicity induced by various mutagens.[108] A recent review on the pharmacological effects of *Glycyrrhiza* sp. described the broad-spectrum of bioactivities of **55** and **56**, including anti-inflammatory, antiviral, hepatoprotective, antitumor, and immunomodulatory.[109] For details about prior studies on antitumor activities of **55** and **56**, see the reviews by Wang and Nixon[108] and Asl *et al.*[109]



Although several studies have found that GA demonstrates cytotoxic or apoptotic activity, most of the results have shown only moderate or low potency. Thus, investigation has focused more on the preparation of active derivatives and chemosensitizing activity. Two 56 analogues, **57** and **58**, which possess a C-3 alkoxyimino group and a C-29 carboxylic acid or methyl ester, showed slightly stronger antiproliferative and apoptotic activities than **56**. The GI_{50} value improved from 63 μM to 19 μM against HL-60 cells. However, the C-29 free acid (**58**) is important, because the methyl ester analogue (**57**) was less potent in the apoptosis assay.[110] The application of 2-cyano-1-ene-3-one (CDDO) modification on GA was successful, as methyl 2-cyano-3,11-dioxo-18β-olean-1,12-dien-30-oate (**59**, β-CDODA-Me) was active against HL-60 cells at a sub-micromolar concentration (EC_{50}: 0.93 μM).[96] Another study reported that **59** and the 2-trifluoromethyl derivative (**60**) were more cytotoxic against KU7 (IC_{50}: 0.38–1.59 μM), Panc-1 (IC_{50}: 0.82–1.22 μM), Panc-28 (IC_{50}: 1.14–1.80 μM), and 253JB-V cells (IC_{50}: 0.25–0.67 μM) compared to **56**. The relative potencies of **59** and **60** were dependent on cell line.[111]



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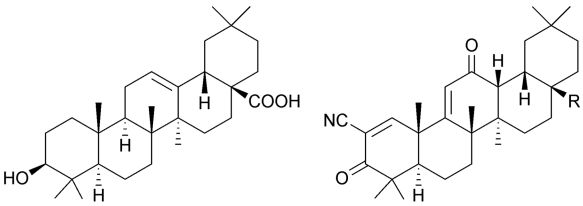
A mechanism study on **59** revealed that its potent antitumor activity may be due to differential induction of two tumor-suppressor genes, Krüppel-like factor-4 (KLF-4) and caveolin-1, in colon cancer cells.[112] Subsequent pro-apoptotic responses were also induced through activation of kinases ATF3, NAG-1, and p21 or through kinase-independent inhibition of AR and PSA, resulting in the growth inhibition of LNCaP cells.[113] Compound **56** showed chemosensitizing effects with various clinical oncology drugs; it enhanced the sensitivity of vinblastine against KB-C2 cells and doxorubicin against KB/MRP cells. In addition, **56** partly reversed multidrug resistance in P-gp-expressing cells (KB-C2) or multidrug resistance protein 1 (MRP1)-expressing cells (KB/MRP), by increasing the intracellular accumulation of the antitumor drugs.[114] In an interesting study, chemical conjugates of **56** and paclitaxel were synthesized. However, although the conjugated compounds (**61**) showed better activity than **56**, they were still less potent than paclitaxel itself.[115] Based on these findings, it is likely that glycyrrhetic acid analogues elicit antitumor activity through multiple pathways.

Oleanolic acid (**62**, OA), a well known triterpene occurring in numerous varieties of plants, possesses many biological properties, including anti-inflammatory, trypanocidal, anti-HIV, and cytotoxic activities.[116] In 1988, OA was reported to suppress TPA-induced tumor promotion.[117] Synthetic A-ring modified OA analogues with improved cytotoxicity were pursued, and 2-cyano-3,12-dioxoolean-1,9-dien-28-oic acid (**63**, CDDO) as well as its C-28 methyl ester, CDDO-Me (**64**, RTA402), were designed and synthesized by Honda *et al.* in 1998. Both of these synthetic derivatives strongly inhibited the production of NO induced by IFN-γ in mouse macrophages (IC_{50}: 0.4 nM).[118] Further derivatization of CDDO to yield imidazolides (**65**, CDDO-Im), amides (**66** and **67**), or a dinitrile (**68**, Di-CDDO), significantly increased the anti-NO activity. Among these derivatives, CDDO-Im (**65**), was 100 times more potent than CDDO, with an IC_{50} value of 1 pM.[119] In addition to the strong anti-inflammatory activity, CDDO derivatives were reported to exhibit other bioactivities, including cytoprotection, cancer cell growth inhibition, and apoptosis induction.[120] Preliminary studies confirmed that OAs have the potential to become an important new treatment for multiple forms of cancer, and both **63** and **64** are currently in phase I clinical trials for the treatment of metastatic or unresectable solid tumors or lymphoma. The pharmacological effects induced by OA-related derivatives were summarized in very recent reviews by Liby *et al.*,[120] Sogno *et al.*[121] and Sultana *et al.*[116]



62

63, R = COOH
64, R = COOMe
65, R = CO-Imidazole
66, R = CONHMe
67, R = CONHEt
68, R = CN

Xanifolia-Y (**69**) was isolated from Xanthoceras *sorbifolia*, and several hydrolyzed derivatives (**70**–**72**) were prepared. Glycoside **69**, which has angeloyl groups on C-21 and C-22, was more cytotoxic (IC_{50}: 2.63 μM) to OVCAR3 cells than either the non-esterified glucoside or the di-esterified aglycone (**70** and **71**, IC_{50}: >120 μM and 14.2 μM, respectively). Thus, the ester moieties on C-21 and C-22 are required for the cytotoxicity, while hydrolysis of the trisaccharide slightly lowered activity.[122]

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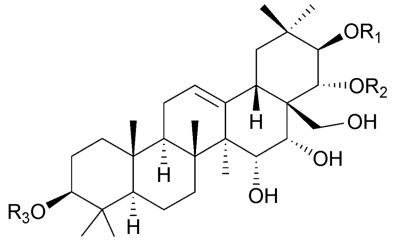
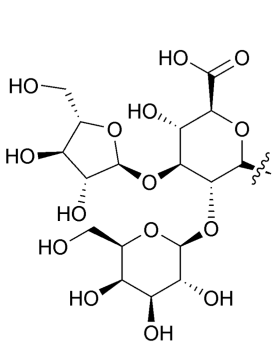
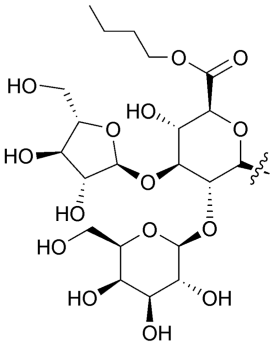
Maslinic acid (**73**), an oleanane triterpene identified from *Crataegus oxyacantha* in 1953,[123] was recently also isolated from apple peel along with the derivatives **74** and **75**. All three compounds were evaluated for antitumor activity, and **74** together with **75** showed minor antiproliferative effects against HepG2 (EC_{50}: 17.9–20.6 μM), MCF-7 (EC_{50}: 20.9–29.2 μM), and Caco-2 (EC_{50}: 8.9–14.2 μM), while **73** showed an effect only on the Caco-2 cell line (EC_{50}: 15.4 μM).[124] Compound **73** was also isolated quantitatively from olive fruit, but showed only a weak anti-proliferative effect against the HT-29 cell line (EC_{50}: 101.2 μM) without any necrotic effects.[125] 25-Hydroxy-3-oxoolean-12-en-28-oic acid (**76**, amooranin) was isolated from the stem bark of *Amoora rohituka*. It was cytotoxic against the SW620 cell line (IC_{50}: 6.2 μM) and delayed tumor growth rate in SW620 xenografts in nude mice. Concurrently, a microarray study of **76** showed that it caused down-regulation of VEGF and JUN genes, which are associated with angiogenesis and antiproliferation of cancer cells, respectively.[126] Capilliposide B (**77**), an epoxy-oleanane saponin isolated from *Lysimachia capillipes*, was cytotoxic against human A-2780 cells, with an IC_{50} value of 0.08 μM.[127] In a semi-synthetic approach,[128,129] analogues were prepared from **77** and screened for cytotoxicity. However, only the 3-*O*-β-D-glucopyranoside (78) and 3-*O*-β-D-galactopyranoside (**79**) derivatives showed enhanced antitumor activity (IC_{50}: 30–40 μm).[128] Two D:C-friedooleanane-type compounds (multiflorane-type), **80** and **81**, isolated from the stems of *Lagenaria siceraria*, showed significant cytotoxicity toward the human SKHEP-1 hepatocellular cancer cell line with IC_{50} values of 8.0 and 4.6 μm, respectively.[130]



69, R_1 = R_2 = angeloyl; R_3 = trisaccharide
70, R_1 = R_2 = H; R_3 = trisaccharide
71, R_1 = R_2 = angeloyl; R_3 = H
72, R_1 = Ac; R_2 = angeloyl; R_3 = trisaccharide



Trisaccharide of **69** and **70**



Trisaccharide of **72**

2.3 The lanostane group

Ganoderic acid D (**82**) isolated from *Ganoderma lucidum* was assessed for anti-proliferation activity and showed an IC_{50} value of 17.3 μm against human cervical carcinoma cells (HeLa). Furthermore, the **82**-treated HeLa cells were arrested at the G2/ M phase of the cell cycle with apoptosis. A simultaneous proteomic study led to the identification of 21 genes regulated by **82**, while the 14-3-3 protein-related genes may play an important role for **82**-induced cytotoxicity.[131] Ganoderiol F (**83**) derived from *Ganoderma amboinense*, was found to inhibit proliferation of cancer cell lines, including chronic myelogenous leukemia (K562,

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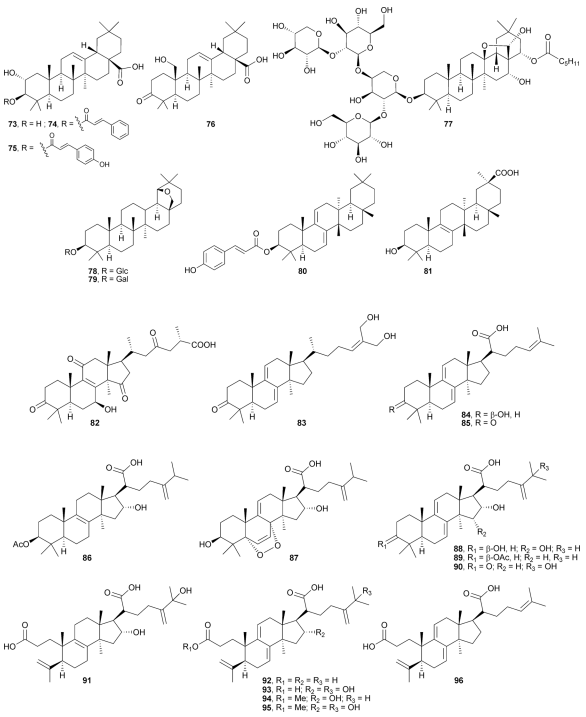
IC_{50}: 4 μm) and hepatocellular carcinoma (HepG2 and Huh7, IC_{50}: 17 μm and 8.5 μm, respectively). Activation of MAPK/ EKR and up-regulation of CDK inhibitor p16 were found in early stages of treatment with **83** and were presumed to cause cell-cycle arrest at the G1 phase and trigger premature senescence of HepG2 cells.[132] Dehydrotrametenolic acid (**84**), a lanostane triterpene isolated from the sclerotium of *Poria cocos*, selectively inhibited H-ras-transformed J82 cells and induced apoptosis through the caspase-3 pathway. Cells treated with **84** were arrested at the G2/M phase and accumulated at the sub-G1 phase, with a high GI_{50} value of 40 μm. Compound **84** also regulated the expression of H-Ras, Akt, and ERK, which are the downstream proteins of H-Ras signaling pathways.[133] In addition, a subsequent study of the same fungus yielded 12 lanostane triterpenes (**85**–**96**), which showed inhibitory effects in the EBV-EA activation assay in Raji cells. Compounds **90** and **96** also showed inhibitory effects in DMBA- and TPA-mediated *in vivo* murine skin tests.[134]



Impatienside A (**97**) and bivittoside D (**98**), two lanostane-type triterpenes containing C-3 hexasaccharide moieties, were isolated from the sea cucumber *Holothuria impatiens*. The two glycosides exhibited *in vitro* cytotoxicity equal or slightly better than those of the clinical antitumor drug etoposide (VP-16) against seven different human tumor cells, including colon cancer (HCT-116 and HT-29), lung cancer (A549), hepatoma (HepG2), prostate cancer (DU145), breast cancer (MCF-7), and nasopharyngeal cancer (KB), with IC_{50} values of 0.25–1.9 μm.[135]

Cucurbitane-type triterpenes, isomers of lanostanes, constitute a group of diverse substances that are known for their bitterness and toxicity. They were isolated initially from Cucurbitaceae plants and were later found in other plant families. Besides cytotoxicity and anticancer activity, cucurbitacins also exhibit other wide ranging *in vitro* or *in vivo* pharmacological effects, such as purgative, anti-inflammatory, and anti-fertility. However, these compounds have had only very limited usage due to their non-specific toxicity. The distribution, structure characterization, and bioactivities were reviewed by Chen *et al.* in 2005.[136] More recent studies showed that cucurbitacin B (**99**) possessed weak inhibitory

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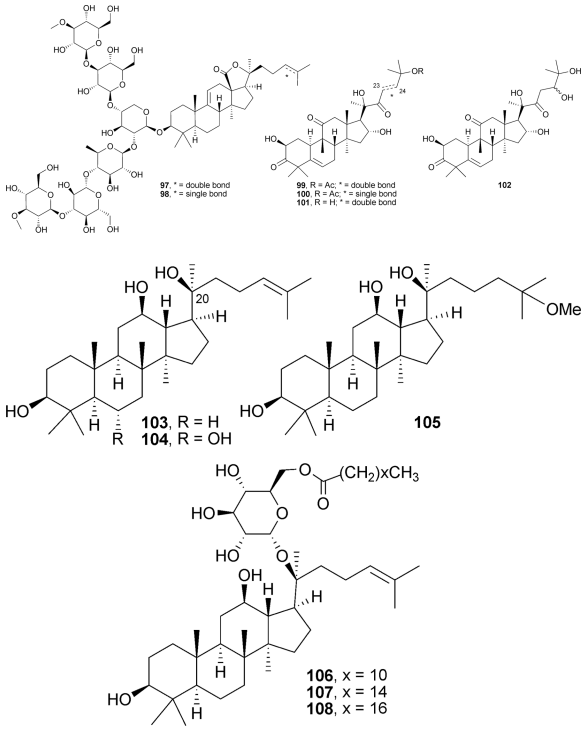
effects on laryngeal squamous cell carcinoma (Hep-2, IC_{50}: 39.06 μm), which may be due to the inhibition of STAT-3, a transcription activator in cell growth.[137] 23,24-Dihydrocucurbitacin B (**100**), isolated from roots of *Trichosanthes kirilowii*, inhibited the proliferation of human breast cancer cells (Bcap37, IC_{50}: 1.5 μm) and arrested the cell cycle at the G_2/M phase. The antiproliferation activity was reduced by the caspase-family inhibitor Z-VAD-FMK, suggesting a mitochondria-dependent pathway.[138] Cucurbitacins D (**101**) and J (**102**) elicited anti-proliferative effects on both hepatocellular carcinoma BEL-7402 cells (IC_{50}: 1.41 and 1.37 μm, respectively) and malignant melanoma SK-MEL-28 cells (IC_{50}: 1.22 and 1.28 μm, respectively).[27]



2.4 The dammarane–euphane group

Ginsenosides are a series of compounds comprised of more than 60 triterpenes and related glycosides isolated from the leaves, stems, berries, and roots of different *Panax* species. Recently, ginsenosides from natural resources were evaluated for their antitumor activity. However, compared to other triterpenes, most ginsenosides showed low to no cytotoxicity (IC_{50}: >20 μm) against various cancer cell lines.[139–144] The anti-angiogenic properties of 20(S)-protopanaxadiol (**103**) and 20(*S*)-protopanaxatriol (**104**) were evaluated in an *in vitro* angiogenesis assay using HUVECs, in which the compounds demonstrated strong anti-proliferative activity (EC_{50}: 2.16–6.64 μm).[142] Furthermore, 20(*S*)-25-methoxyprotopanaxadiol (**105**) induced apoptosis and cell cycle arrest in the G1 phase, inhibited proliferation of T98G, HPAC, A-549, H1299 and PC-3 cell lines (IC_{50}: 5.0, 5.8, 5.7, 4.9, and 5.8 μm, respectively), and was 5- to 15-fold more potent than **104**.[145,146] In addition, three semi-synthetic derivatives with a C-20 sugar moiety (**106**–**108**) showed significant cytotoxicity against MCF, SK-MEL-2, and B16 cancer cell lines[147] (see Table 2).

25-Methoxyhispidol A (**109**), a tirucallane triterpene isolated from the fruit of *Poncirus trifoliata*, demonstrated a slight antiproliferative effect (IC_{50}: 21.0 μm) against the SKHEP-1 cell line, which was postulated to occur through arrest in the G0/G1 cell cycle and induction

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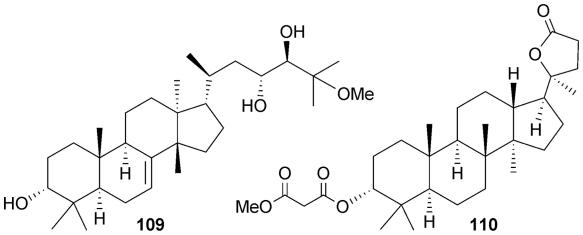
of apoptosis.[148] The dammarane derivative **110** was isolated from the flower spikes of *Betula platyphylla*.[81,149] Compound **110** inhibited the efflux of rhoda-mine 123 KB-C2 cells, implicating MDR-reversing effects by modulating P-gp.[149]



Five dichapetalin-type triterpenoids, dichapetalins A (**111**), I (**112**), J (**113**), K (**114**), and L (**115**), were isolated from the stem bark of *Dichapetalum gelonioides*. Compounds **111**–**113** showed selective inhibitory activity (IC_{50}: 0.3–0.8 μm) against the SW626 human ovarian cancer cell line, while **114** and **115** showed broader cytotoxicity against Lu1, LNCaP, SW626, MCF-7, and HUVEC cell lines (IC_{50}: 1.6–14.2 μm).[35] Acutissimatriterpenes A, B, and E (**116**–**118**) were isolated from the aerial parts of *Phyllanthus acutissima*.[150] Compounds **116** and **117** exhibited cytotoxicity only against P-388 tumor cell line, while compound **118** showed cytotoxicity against P-388, MCF-7, and Lu-a tumor cell lines (IC_{50}: 0.007–7.100 μm). Most impressively, **118** demonstrated remarkable cytotoxicity against P-388 (IC_{50}: 0.007 μm), and was more potent than ellipticine, the positive control (IC_{50}: 0.813 μm).[150] However due to the complex structures and the limited extent of the study, SAR conclusions could not be readily established for dichapetalin-type triterpenoids.

2.5 Other triterpenoids

Quinonoid triterpenes—Celastrol (**119**), a quinone methide triterpenoid, was isolated recently from *Celastrus orbiculatus*,[151] *Cheiloclinium cognatum*,[152] and *Maytenus chuchuhuasca*.[153] It was already known that celastrol exhibits anti-inflammatory,[154,155] antioxidant,[155] neuro-protective,[156,157] and anti-infective properties, and its strong cytotoxic effect was reported as early as 1981.[158] Very recent studies showed that **119** was cytotoxic against Panc-1 pancreatic cancer cells (IC_{50}: 3 μm) *in vitro*, active against Panc-1 xenografts *in vivo* in mice, and inhibited tumor metastasis in the RIP1-Tag2 transgenic mouse model of pancreatic islet carcinoma.[159]

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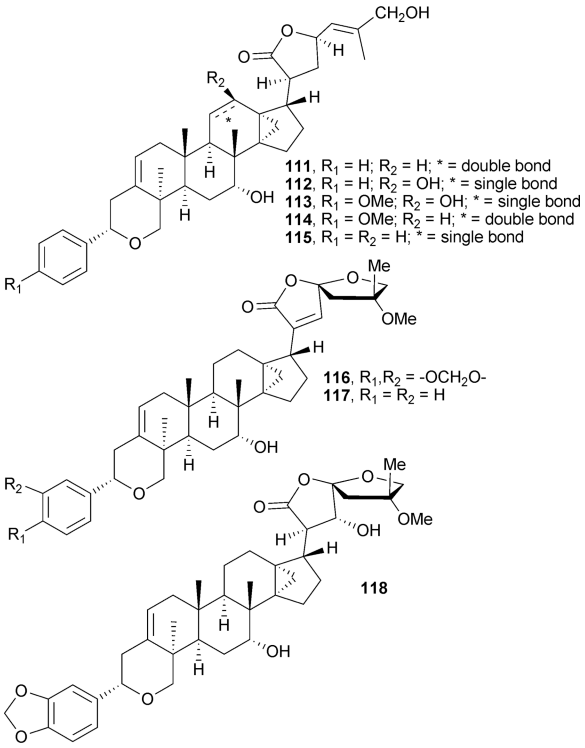

Previous investigation on the strong antitumor effect of **119** prompted a series of studies on its molecular target. It enhanced the cytotoxic effects of TNF, paclitaxel, and doxorubicin, as well as the TNF-κB pathway and NF-κB-regulated gene products.[160] Further pharmacological study showed that **119** inhibited the activation of NF-κB by blocking the phosphorylation and degradation of IkB kinase in the upstream NF-κB signal transduction cascade.[151] Both **119** and gedunin (**136**) were found to inhibit HSP90 function by acting outside the ATP-binding pocket, which is similar to the action of the existing drugs cisplatin and novobiocin.[159,161,162] A concurrent study revealed that **119** suppressed the activation of aryl hydrocarbon receptor-dependent gene expression in oral leukoplakia (MSK-Leuk1) cells, which implicates a chemopreventive effect.[163] Investigation of its anti-angiogenesis effect revealed that **119** suppressed angiogenesis by acting on the VEGF tyrosine kinase receptors, VEGFR-1 and VEGFR-2, but not VEGF itself.[164] Compound **119** also showed both *in vitro* and *in vivo* chymotrypsin-like proteasomal inhibitory activity toward purified proteasome (20S and 26S proteasome, IC_{50}: 2.5–5 μm) in PC-3 or LNCaP cells, and inhibited PC-3 xenografted tumors in nude mice.[165]

Subsequent SAR studies on semi-synthetic analogues of **119** concluded that the quinone methide moiety is important for cytotoxic activity. Dihydrocelastrol (**120**) and 6-oxo-pristimerol (**121**), derivatives with an aromatized quinone methide moiety, were inactive in both cytotoxicity[166] and anti-tubulin polymerization assays.[153] The C-29 free acid present in **119** is not required for its ability to induce apoptosis; C-29 ester or amide derivatives (**122**) showed an equal or lower potency in inhibiting the growth of human and mouse melanoma tumor cells.[166] Analogues that lack C-29, such as tingenone (**123**) and 22β-hydroxytingenone (**124**), showed lower activity than **119** in *in vitro* tubulin polymerization inhibition and cytotoxicity assays against RPMI8226 cell lines.[153]

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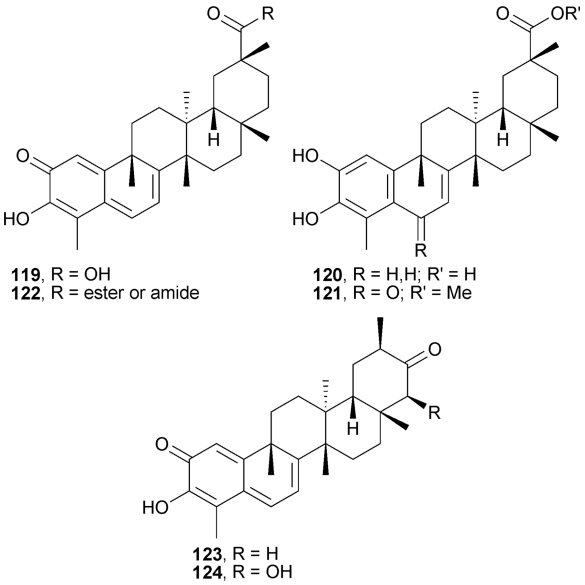

Tetranortriterpenes (limonoids)—Triterpenoids belonging to the limonoid family occur as glucosides and aglycones in fruits of Rutaceae and Meliaceae plant families. They show putative antitumor properties, and have been sufficiently reviewed regarding their distribution,[167] biosynthetic pathway,[168,169] and bioactivity.[170,171] The latest study on the antiproliferative effects of three limonoids, limonin (**125**), nomilin (**126**) and obacunone (**127**), confirmed that, as either aglycones (**125**–**127**) or glycosides (**128**–**130**), these compounds exert versatile action against neuroblastoma cancer cells (SH-SY5Y). They induced apoptosis, arrested the cancer cell cycle at the G1 phase, and showed an aneuploidic effect, which elevated the aneuploid numbers in treated cancer cells compared with untreated ones. Both aglycones and glucosides were toxic to the cells, but aglycones were less effective in causing rapid cell death.[172]

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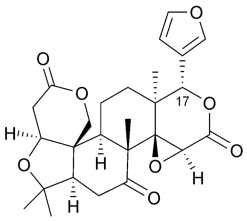
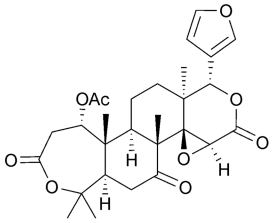
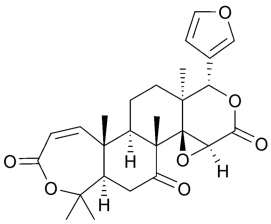
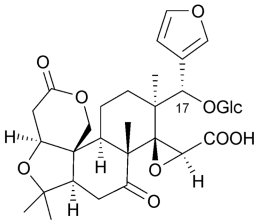
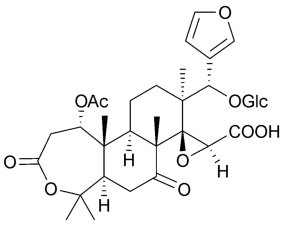
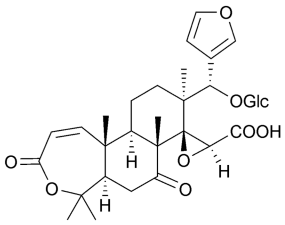




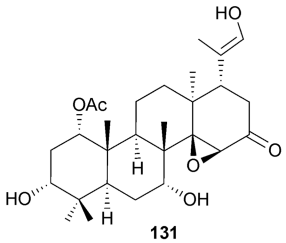


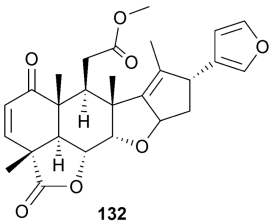


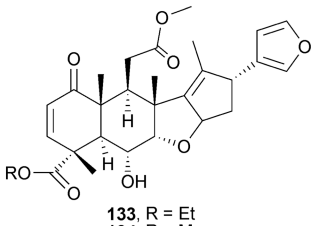




3α,7α-Dideacetylkhivorin (**131**) was isolated from *Khaya senegalensis*, and subsequent cytotoxic screening showed that it was active against SiHa (IC_{50}: 0.11 μM), MCF-7 (IC_{50}: 0.14 μM), and Caco-2 (IC_{50}: 0.07 μM) cancer cell lines.[173] Nimbolide (**132**), a limonoid extracted from the flowers of *Azadirachta indica* (neem tree), exhibited potent cytotoxic activity against U937 (IC_{50}: 1.24 μM), HL-60 (IC_{50}: 1.12 μM), and THP1 (IC_{50}: 1.42 μM) cells and antiproliferation activity against B16 (IC_{50}: 1.74 μM) cell lines. In a follow-up study using the U937 cell line, **132** increased the number of aneuploid cells and the appearance of annexin V positive cells, implicating the occurrence of cell arrest and apoptosis, correspondingly.[174] Two nimbolide derivatives, **133** and **134**, were synthesized from **132**, but showed weak activity in the brine shrimp lethality bioassay, indicating the importance of the lactone ring.[175]







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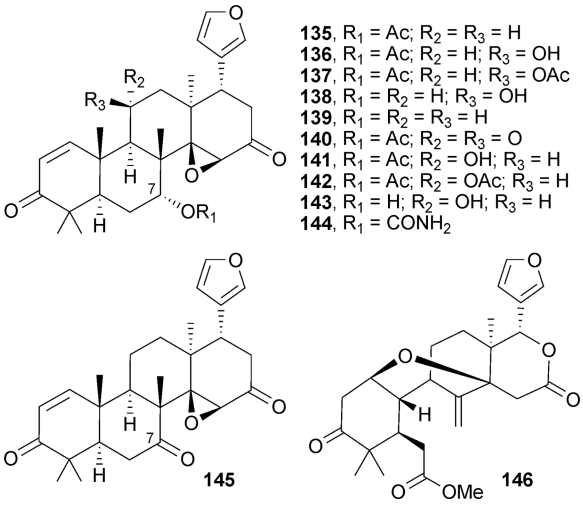
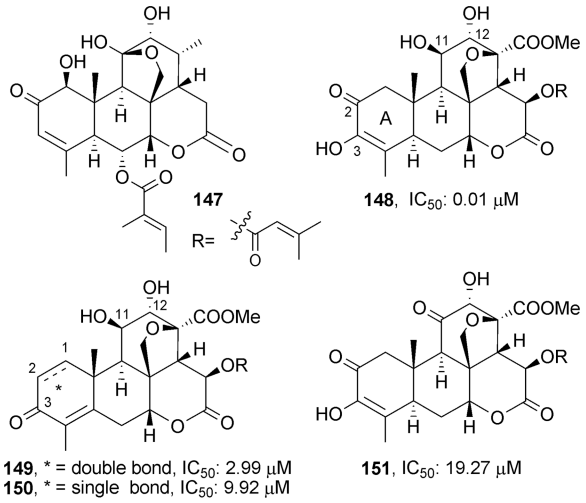
Gedunin (**135**), a limonoid with antimalarial, insecticidal, and antitumor activities, was recently isolated from *Xylocarpus granatum*[176] and *Cedrela sinensis*.[177] It exerted weak antitumor activity against the CaCo-2 cell line, with an IC_{50} value of 16.83 μM.[176] However, **135** and its derivatives **136**–**140** showed moderate cytotoxicity against P-388 murine leukemia cells, with IC_{50} values ranging from 6.0–17.1 μM. In the same study, **141**–**143** exhibited very weak or no activity (IC_{50}: >116 μM), suggesting that an oxygenated functionality at the 11α-position is critical.[177] Further modification at C-7 on **135** gave two active analogues with C-7 carbamate (**144**) and ketone (**145**) groups. These compounds demonstrated antiproliferative activity comparable to **135**, and acted by modulating heat shock protein (Hsp90) in MCF-7 and SkBr3 cells.[178] Methyl angolensate (**146**), a natural tetranortriterpenoid derived from the root callus of *Soymida febrifuga*,[179] possessed low cytotoxic activity (IC_{50}: 100.0 μM), but did induce apoptosis by triggering the intrinsic pathway.[180]



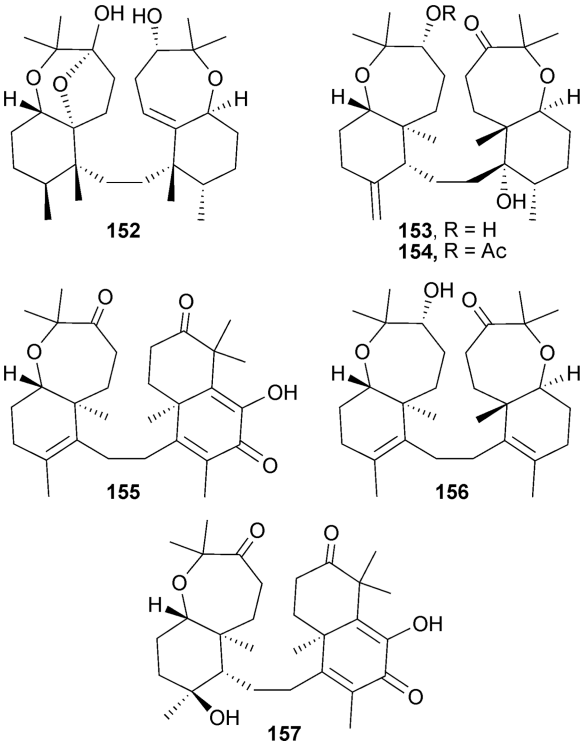
Quassinoids—Quassinoids are bitter constituents and secondary metabolites exclusively of Simaroubaceous origin. They are regarded biogenetically as degraded triterpenoids. Quassinoids have diverse bioactivities including antifeedant, insecticidal, herbicidal, antiparasitic, antimalarial, and antitumor effects.[181]

As early as the 1970s, reports ascribed a wide range of antitumor activity to bruceantin, a quassinoid triterpene, which elicited major interest in quassinoids as promising lead drugs. However, the complex chemical structures of quassinoids have limited their anticancer potential. For more details, see the review by Vieira *et al.*[181]

6α-Tigloyloxychaparrinone (**147**) was isolated from *Ailanthus integrifolia* in 1978,[182] and its antitumor activities have been reported.[183,184] More recent studies led to the isolation of **147** from *A. altissima*. It showed inhibitory effects on hypoxia-induced VEGF, erythropoietin expression, and the activation of HIF-1α, a transcription factor protein that promotes tumor cell adaptation and survival under hypoxic conditions.[185] Brusatol (**148**) showed cytotoxic activity against P-388 murine cancer cells, with an IC_{50} value of 0.012 μM. The A-ring modified compounds **149** and **150** showed reduced activity, indicating that the C-2 enolic oxygen is essential for activity. The 11-ketone analogue **151** showed even weaker activity, indicating that a β-hydroxy group at C-11 is also important.[186]



Triterpenes from marine sources—Numerous sodwanone triterpenes have been purified from *Axinella* species. Among them, sodwanone V (**152**) inhibited activation of HIF-1 in T47D (IC_{50}: 15 μM) and PC-3 (IC_{50}: 15 μM) cells. It also showed weak cytotoxicity against MDA-MB-231 breast tumor cells (IC_{50}: 23 μM). 10,11-Dihydrosodwanone B (**153**) showed moderate cytotoxicity against T47D cells (IC_{50}: 22 μM). Four derivatives, **154**–**157**, inhibited hypoxia-induced HIF-1 activation in T47D cells (IC_{50}: 20–25 μM).[187]



Two sipholane-type triterpenes, sipholenol A (**158**) and sipholenone A (**159**), were isolated from the marine sponge *Callyspongia siphonella*. They showed cytotoxic activity against the MCF-7 breast cancer cell line, with IC_{50} values of 1.2 and 0.9 μM, respectively. At a dose of 0.026 μM per pellet, **159** also showed anti-angiogenic activity in the chorioallantoic

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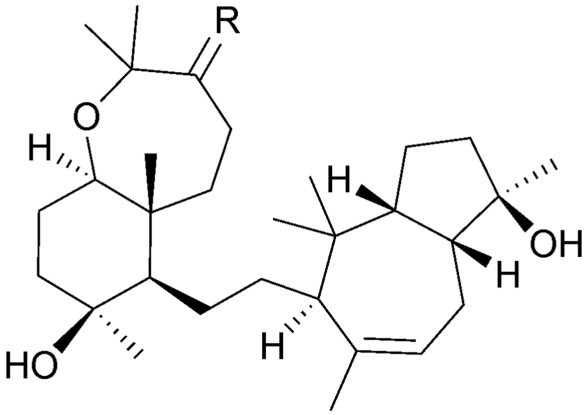
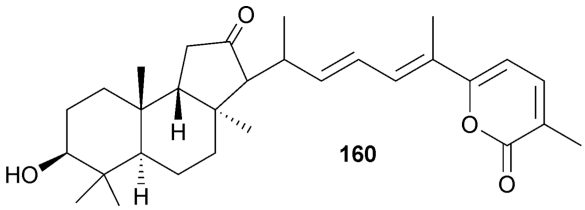
membrane (CAM) assay.[188] In a chemosensitization study, **158** potentiated the cytotoxicity of the antitumor drugs colchicine, vinblastine, and paclitaxel against MDR nasopharyngeal cancer cell lines (KB-C2 and KB-V1), by inhibiting P-gp(ABCB1)-mediated drug efflux.[189]



158, R = α-OH, H
159, R = O

Jaspolide B (**160**), a novel isomalabaricane-type triterpene isolated from marine sponges, *Jaspis* spp,[190] exhibited cytotoxicity toward hepatoma (Bel-7402, IC_{50}: 29.1 μM; HepG2, IC_{50}: 29.5 μM) and human promyeloleukemic (HL-60, IC_{50}: 0.78 μM) cell lines.[191,192] Subsequent studies showed **160** induces apoptosis and cell cycle arrest in HL-60 at the G2/M phase[191] and in Bel-7402 at the G1 phase.[192]



160

3 Anti-HIV effects of triterpenoids

3.1 The lupane group

In 1994, the authors' Natural Products Research Laboratories first discovered that betulinic acid (1, BA) showed an inhibitory effect against HIV-1_{IIIB} replication, with an EC_{50} value of 1.4 μM.[193] Since then, betulinic acid has been used as a pre-eminent molecular scaffold in the development of triterpene analogues as anti-HIV drugs. Systematic structural modifications were carried out on the C-3 hydroxyl, A-ring, C-19 isopropenyl group, and C-28 carboxyl moiety, which led to the discovery of many potent anti-HIV agents (Table 3).[194,195]

The C-3 hydroxy group can be readily acylated with a wide variety of anhydrides and acid chlorides. Such modification resulted ultimately in the identification of bevirimat (3-*O*-3′,3′-dimethylsuccinyl BA, **161**), which displayed a significant anti-HIV EC_{50} value of 0.35 nM.[196] The SAR study also showed that an ester functionality at C-3, an appropriate length of the C-3 side chain, a terminal carboxylic acid moiety, and dimethyl substitution at the C-3′ position are critical for the enhanced antiviral potency of **161**. Further SAR demonstrated that, within the 3′-dimethyl moiety, the 3′*S*-methyl contributed more towards the activity, because 3′*S*-monomethylsuccinyl-substituted BA (3′*S*-MSB, **162**) and **161**

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showed similar antiviral potency (EC_{50}: 8.7 and 1.3 nM, respectively), while 3′*R*-MSB (**163**) showed much reduced activity (EC_{50}: 0.12 μM).[197]

Mechanism of action studies revealed that **161** retained its nanomolar antiviral potency against HIV-1 isolates resistant to reverse transcriptase (RT) and protease (PR) inhibitors. To define the target of **161** (bevirimat), scientists from Panacos Pharmaceuticals Inc. and the National Institutes of Health characterized the virus produced by cells treated with the compound.[198] The studies showed that **161** inhibited the processing of the viral Gag polyprotein at a specific step, the conversion of the capsid precursor p25 to mature capsid (CA) p24, in a dose-dependent manner.[198] The impaired cleavage of p25 to p24 led to the production of morphologically defective, non-infectious, immature viral particles (Fig. 2). Therefore, **161** was designated as amaturation inhibitor (MI),a new class in the antiretroviral family. It is currently in Phase IIb clinical trials and will enter Phase III clinical trials in 2009.

Conversely, C-28 ω-aminoalkanoic acid derivatives of **1** were discovered to function by blocking the viral entry into the host cells.[199,200] Incremental chain lengthening significantly influenced the anti-HIV potency of the derivatives, while the introduction of a second aminoalkanoic acid at the end of the C-28 side chain could further modulate the antiviral potency.[195] This research led to the discovery of RPR103611 (**164**),[199] a statine derivative, which inhibits the infectivity of several HIV-1 strains with EC_{50} values in the range of 0.05–2 μM, and **9** (IC9564),[201] a stereoisomer of **164**, which showed equipotency in the antiviral testing. A43-D (**165**) was designed with a slightly simplified C-28 substituent.[202] It also showed similar anti-HIV activity compared to **9** and **164**.

A mechanism of action study discovered that C-28-modified BA analogues function at a post-binding step necessary for virus entry to the host cell. Detailed study found that **9** induced a nonproductive gp120 conformation that is not able to trigger a conformational rearrangement in gp41 for membrane fusion.[203] Evidence also indicated that **9** can target the V3 loop of gp120, a domain involved in chemokine receptor binding.[204] The exact binding target of triterpene derivatives is still under investigation.

Modification of the C-19 isopropenyl group showed little effect on the anti-HIV activity. Neither saturation of the 20(29) double bond nor allylic substitution at C-30 through an ether or thioether linkage influenced the anti-HIV activity of the **1** derivatives significantly.[205] Further research demonstrated that the C-30 position serves as a good place to incorporate water-solubilizing moieties and to increase the hydrophilicity of this compound class.[205]

Interestingly, as indicated, the anti-HIV-1 targets of triterpene analogues can vary depending on the side chain modification positions. C-28-modified analogues of **1** are potent HIV entry inhibitors, while C-3-modified derivatives function by blocking virus maturation. A combination of these two modifications led to the identification of A12-2 (**166**), a bifunctional HIV inhibitor that interferes with both viral entry and maturation.[202] Compounds **167** and **168**, in which a secondary amine forms the C-28 amide bond, exhibited significantly increased metabolic stability in pooled human liver microsomes.[205] Compounds **166**–**168** showed very potent anti-HIV activity, which was slightly better than that of **161**. Gerrish *et al.* synthesized another series of 3,28-disubstituted **1**-analogues.[206] These compounds contained a dimethylsuccinyl ester side chain at C-3 and variously substituted benzyl and phenethyl amides at C-28. Several compounds in this series showed potent anti-HIV activity, and **169** and **170** showed the best pharmacokinetic/pharmacodynamic (PK/PD) properties.[206] Generally, substitutions at the *ortho*-position of the benzyl or phenyl ring provided the best activity. The 3,28-dimodified derivatives may

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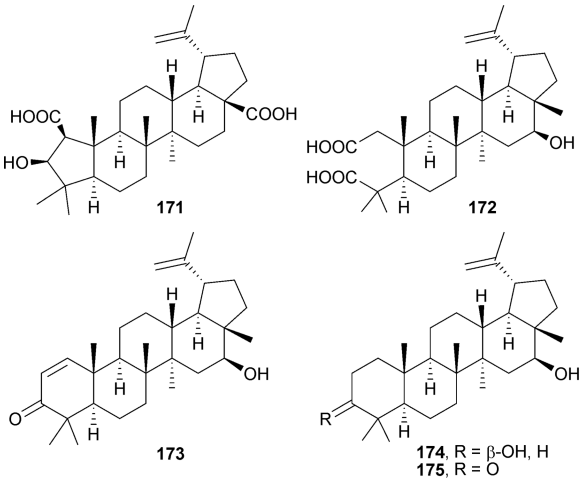
serve as attractive promising leads to develop a next generation of **1**-derived HIV-1 inhibitors as clinical trials candidates.

2β-Carboxyl-3β-hydroxyl-norlupA(1)-20(29)-en-28-oic acid (**171**), a lupane-like triterpene with a rearranged five-membered A-ring, was isolated from the thorns of *Gleditsia sinensis*. It showed significant anti-HIV activity, with an EC_{50} value of <0.13 μM.[207] The fact that **171** differs from **1** only in the A-ring configuration suggests that A-ring functionalities are important pharmacophores for the antiviral activity of the lupane-type triterpenes.

A new 2,3-seco-lupane triterpene, 16β-hydroxy-2,3-seco-lup-20(29)-ene-2,3-dioic acid (**172**), was obtained during a search for antiviral agents in the stems of *Stauntonia obovatifoliola*.[208] Compound **172** exhibited good anti-HIV-1 protease activity (EC_{50}: 17.8 μM), compared with the control **62** (EC_{50}: 54.38 μM), a known HIV-1 protease inhibitor.[208] This result suggested that a seco A-ring with dual polar moieties may increase the antiviral protease activity of triterpenes. In a concurrent study, lupane-, 30-noroleanane-, and oleanane-type triterpenes showed similar anti-HIV protease activity during testing. When analyzing the structures more carefully, it was discovered that the 16β-OH group is important to the enhanced antiviral potency of lupane triterpenes, as seen with compounds **172**–**175**.



3.2 The ursane and oleanane groups

The oleanane-type triterpene maslinic acid (**73**) inhibits the HIV-1 protease. In order to further explore the antiviral activity, several different α- and ω-amino acids (single, dipeptide, or tripeptide) were coupled at the C-28 position of **73** by using both solution- and solid-phase synthetic methods. However, only compounds **176** [with 11-aminoundecanoic acid (11AUA) at C-28] and **177** (with a C-28 conjugate dipeptide of 11AUA and L-valine) showed approximately 50% inhibition activity against virus replication at 10 μM. These derivatives showed no cytotoxicity, although **73** itself displayed both cytotoxic and antiviral activities.[209]

Prior research on glycyrrhetic acid (**56**) and its synthetic derivatives mainly led to negative results.[210,211] The modifications focused on substitutions of the C-3 hydroxy and C-30 carboxylic acid groups. Because the rigid triterpene scaffold determines the relative position of the functional side chains, the skeleton could be very important to the anti-HIV and other bioactivities. Therefore, the distance from the hydroxy group to the carboxylic moiety and the dihedral angles of the D/E rings were predicted using modeling software. The results

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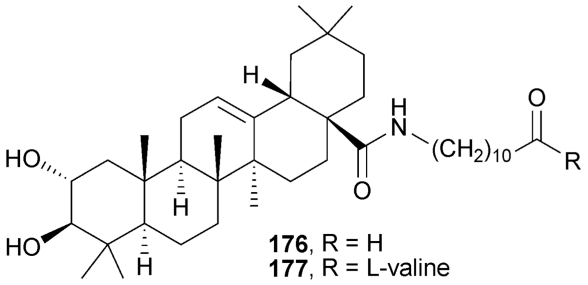
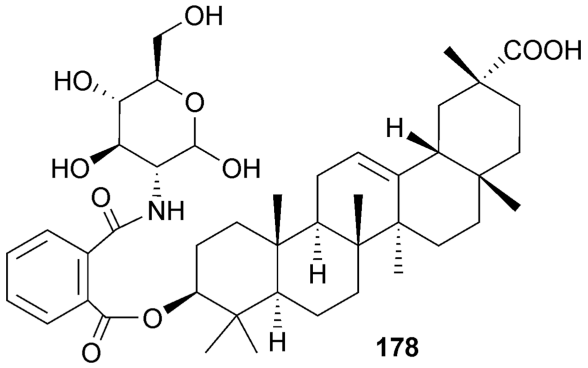
provided a possible explanation for why analogues of **56** showed fewer anti-HIV effects than analogues of betulinic (**1**) or moronic acid (**181**).[210,211]



A recent paper reported the synthesis and anti-HIV activity of a group of analogues of α-D-glucosamine-conjugated glycyrrhetic acid (**56**).[212] The glucosamine was linked to the 3β-hydroxy group through a spacer containing phthalic, maleic, or succinic acid residues. Although such modifications slightly increased the anti-HIV activity of **56**, the antiviral potency of these derivatives remained only moderate. The most potent analogue 3-*O*-[3-(*N*-2-deoxy-α-D-glucopyranos-2-yl)-carbamoyl]-phthaloyl-11-deoxy-glycyrrhetic acid (**178**) had an anti-HIV EC_{50} value of 2.0 μM.[212]



The anti-HIV and other biological activities of oleanolic acid (**62**, OA) and its derivatives were reviewed by Sultana *et al.* in 2007.[116] Basically, OA was identified as an anti-HIV principle, because it inhibited HIV-1 replication with an EC_{50} value of 3.7 μM and a therapeutic index (TI) of 12.8.[213] Modification of OA at the C-3 position led to the discovery of 3-*O*-3′,3′-dimethylsuccinyl-OA (**179**), which had significant antiviral EC_{50} (0.86 nM) and TI (22 400) values.[213] However, due to differences in the screening system, the reported activity of **62** may vary in different publications.[211] The mechanism of action of **179** is similar to that of **161**, which functions as a maturation inhibitor and blocks the cleavage of p25 to p24, resulting in the production of morphologically defective, non-infectious HIV particles. The SAR of 3-*O*-acyl OAs with different succinyl or glutaryl substitution showed similar trends compared with 3-*O*-acyl BA analogues, suggesting that the C-3 side chain is a very important pharmacophore, while the triterpene backbone may serve as a docker allowing the side chains to interact with the targets.

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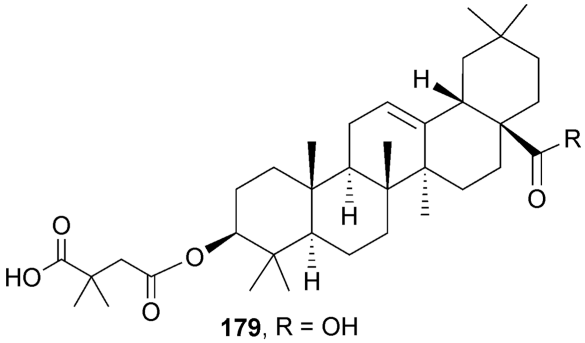
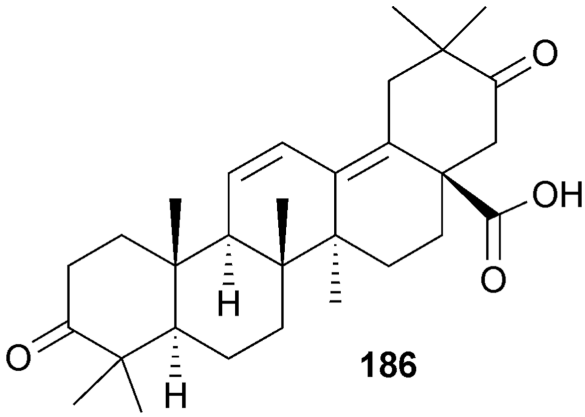


Previously, the optimal C-3 and C-28 side chains were identified in bi-functional betulinic acid (BA) analogues. Therefore, to extend the research focus on the replacement of triterpenoid docker, some 3,28-disubstituted OA derivatives were also prepared.[210] Compound **180**, an OA derivative with 1,7-dia-minoheptane linked at the C-28 position and 3′,3′-dimethyl-succinyl linked at the C-3 position, showed anti-HIV activity, with an EC_{50} value of 0.95 μM.[210] This activity is lower than the identically substituted BA analogue, **166** (EC_{50}: 0.0026 μM), indicating that BA is a better-fit docker than OA.

Moronic acid (**181**, MA) was isolated from Brazilian propolis, a herbal medicine used worldwide. It exhibited significant anti-HIV activity with an EC_{50} value of 0.2 μM and TI of 186.[214] In 2006, the authors' group reported the discovery of a series of MA derivatives that exhibited remarkable anti-HIV potency. Compounds **182**–**184**, which contain C-3 3′,3′-dimethylsuccinyl substitution and different C-28 amide side chains, exhibited potent anti-HIV activity in H9 lymphocytes with EC_{50} values of 0.017, 0.0156, and 0.007 μM, respectively (Table 4).[211] These activity results are similar to those of **161** (EC_{50}: 0.007 μM), a drug candidate that is currently in phase IIb anti-AIDS clinical trials. Another 3,28-disubstituted MA derivative (**185**) was synthesized and had an antiviral EC_{50} value of 0.055 μM (Table 4).[210] Mechanism of action study revealed that 3,28-disubstituted betulinic acid or moronic acid analogues exhibit both anti-fusion and anti-maturation activity. Thus, they were designated as bifunctional triterpenes.[208,213] From the SAR, it was discovered that a longer C-28 side chain (as in **184** and **185**) is helpful for enhanced antiviral potency.



Another oleanane-type triterpene, papyriogenin A (**186**), was isolated from the flowers, pith, leaves, and fruit of *Tetrapanax papyriferus*. It showed antiviral activity, with an EC_{50} value of less than 1.7 μM in HIV-1IIIB-infected H9 lymphocytes.[215]

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C-3-modified ursolic acid (UA),[211,216] as well as 3- and 28-modified UA analogues (**187**–**189**),[210,211] were synthesized and evaluated for anti-HIV activity (Table 5). The C-3-(3′,3′-dimethylsuccinyl)- and C-3-(3′,3′-dimethylglutaryl)-substituted derivatives of UA (**188** and **189**) exhibited anti-HIV replication, with EC_{50} values of 0.08 and 0.68 μM, respectively.[211] Compound **187**, which was evaluated with a different assay system, also displayed anti-HIV activity, with an EC_{50} value of 0.23 μM.[210] When the activities of triterpenes with the same side chain but different scaffolds were compared, it was discovered that, among the synthesized compounds, the most effective molecular scaffold for anti-HIV activity remained betulinic acid (**166**, EC_{50} value: 0.0026 mM), followed by moronic, ursolic, and oleanolic acids.[210]

In addition, some a-aminophosphonates were conjugated to the C-28 of UA.[217] However, all of the resulting analogues showed zero-to-weak anti-HIV entry activity. The best compound (**190**) inhibited viral entry by only 20% at a concentration of 0.1 μM.[217] This result further proved the conclusion that a longer C-28 side chain is very important for triterpene-derived HIV entry inhibitors, with a carbon chain length of 7–10 being optimal.

3.3 The lanostane group

Plants of the genus *Schisandra* are known to contain dibenzo-cycloctadiene lignans, as well as lanostane and cycloartane triterpenes. In 2003, Sun's group began a phytochemical study of several species of the *Schisandra* genus collected in the Yunnan province of China, which led to the discovery of a series of norcycloartane triterpenoids. During 2006–2008, Sun's group also identified several nortriterpenoids and bisnortriterpenoids from various species of *Schisandra* that possessed weak to moderate anti-HIV-1 activity.[218–220]

Rubriflordilactones A (**191**) and B (**192**) were isolated from the leaves and stems of *Schisandra rubriflora*.[221] They are highly unsaturated rearranged bisnortriterpenoids that contain a biosynthetically modified aromatic D-ring. The anti-HIV activity of both compounds was tested in HIV-1_{IIIB}-infected C8166 cell lines, and their cytotoxicity was evaluated in C8166 and MT-4 cells. Compound **191** showed only weak antiviral potency; however, **192** presented moderate anti-HIV activity, with an EC_{50} of 21.1 μM and TI of 12.39.[221]

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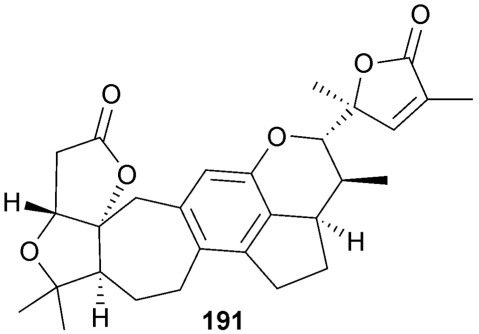

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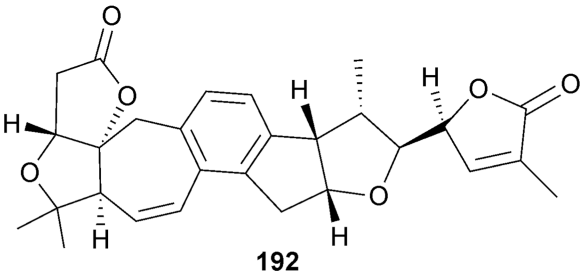
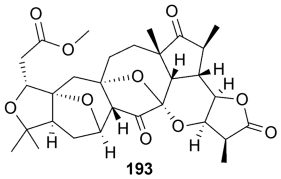


192

Rubriflorins A–C (**193**–**195**), three highly oxygenated nortriterpenoids, were also isolated from the leaves and stems *Schisandra rubriflora*.[222] They feature an opened A-ring. Compounds **193** and **194** exhibited moderate anti-HIV-1 activity, with EC_{50} values of 17.9 and 29.2 μM, respectively, while **195** showed weak HIV-1 inhibition activity, with an EC_{50} value of 143.1 μM.[222] Rubriflorins D–J (**196**–**202**) were found in the same plant shortly after the discovery of **193**–**195**.[223] They also contain an opened A-ring and showed moderate to weak anti-HIV activity, with EC_{50} values ranging from 26.4 to 167.0 μM.[223]



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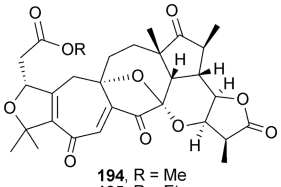
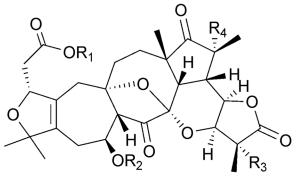


194, R = Me
195, R = Et



196, $R_1 = R_2 = R_3 = R_4 = H$
196, $R_1 = H$; $R_2 = Ac$; $R_3 = R_4 = H$
198, $R_1 = H$; $R_2 = Ac$; $R_3 = OH$; $R_4 = H$
199, $R_1 = Et$, $R_2 = R_3 = R_4 = H$
200, $R_1 = Et$; $R_2 = H$; $R_3 = OH$; $R_4 = H$
201, $R_1 = Et$; $R_2 = H$; $R_3 = R_4 = OH$
202, $R_1 = Me$; $R_2 = R_3 = R_4 = H$

Sphenadilactones A (**203**) and B (**204**) were isolated from the leaves and stems of *Schisandra sphenanthera*.[224] Their structural elucidation was accomplished by extensive NMR and single-crystal X-ray crystallography. However, an erratum was later published to correct the stereochemistry of Me-27, which should have an α- rather than β-orientation.[225] Compound **203** exhibited very weak anti-HIV-1 activity, with an EC_{50} of 237.8 μM in HIV-1_{IIIB}-infected C8166 cells.[224] No obvious cytotoxicity was observed when both compounds were tested against three human tumor cell lines, K562, A549, and HT-29. A minor nortriterpenoid, sphenadilactone C (**205**), was also isolated in a subsequent study of *Schisandra sphenanthera*.[226] It is characterized by the presence of a partial enol structure, and is the first example of an acetamide-bearing highly oxygenated nortriterpenoid from a cycloartane. Compound **205** also exhibited very weak antiviral activity against HIV-1_{IIIB}, with an EC_{50} of 47.8 mM.[226]

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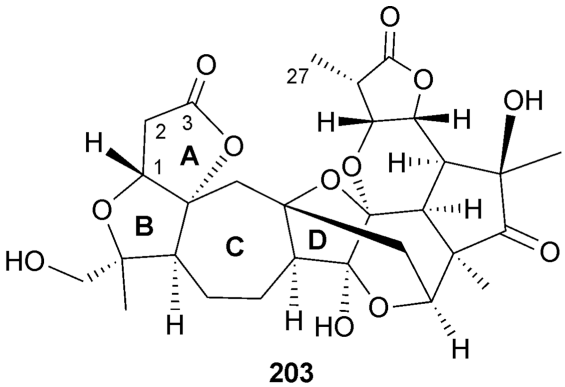
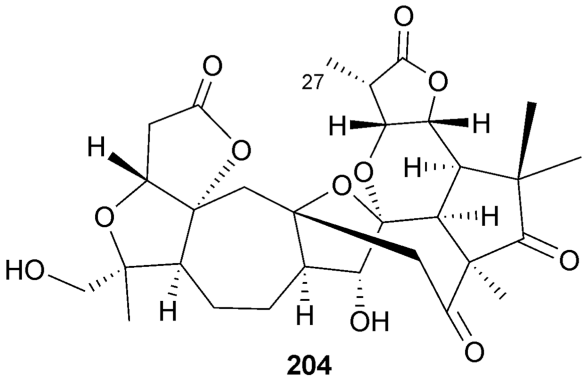


203



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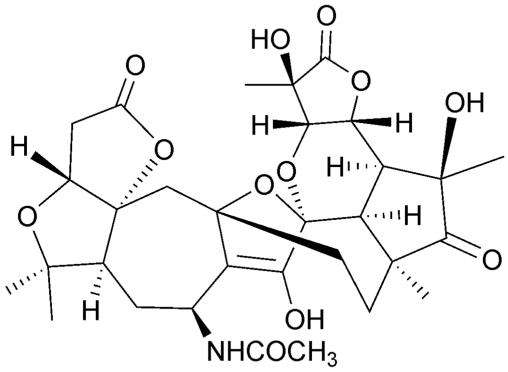
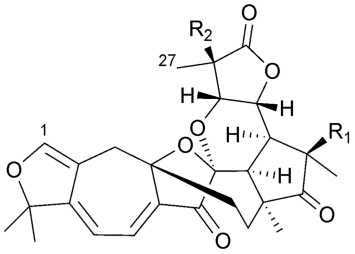


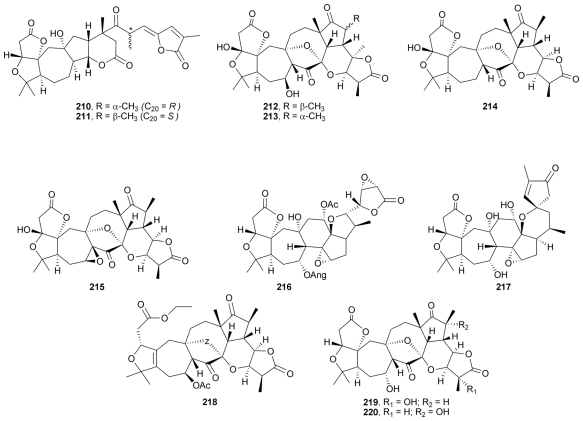
205

Re-investigation of *Schisandra sphenanthera* resulted in the isolation of sphenalactones A–D (**206**–**209**), which have an unusual 27-carbon skeleton derived from cycloartane, due to the loss of C-2, C-3, and CH_3-28.[227] This is the first class in the *Schisandra* species and the first case in the cycloartane triterpenoid family in which C-2 and C-3 are degraded in the molecule. Compounds **208**–**209** demonstrated weak anti-HIV-1 replication activity, with EC_{50} values of 185.1, 153.7, 105.4, and 76.2 μM, respectively.[227]



206, R_1 = OH; R_2 = H
207, R_1 = H; R_2 = OH
208, R_1 = R_2 = OH
209, R_1 = R_2 = H

Schintrilactones A (**210**) and B (**211**), two new nortriterpenoids with modified five-membered D-ring and δ-lactone E-ring, were isolated from *Schisandra chinensis*. Both compounds have a unique carbon skeleton, with an unstable stereogenic center at C-20. The two diastereomers slowly interconvert through an enol intermediate. Compounds **210** and **211** demonstrated anti-HIV-1 activity, with EC_{50} values of 33.9 and 68.2 μM, respectively, compared with AZT as positive control (EC_{50}: 8.46 μM).[228] Nortriterpenoids schindilactones D–G (**212**–**215**) and bisnortriterpenoids wuweizidilactones G (**216**) and H (**217**) were also isolated from the stems and leaves of *Schisandra chinensis*. However, they demonstrated only weak antiviral activity, with EC_{50} values ranging from 32 to 181 μM.[229] Wilsonianadilactones A–C (**218**–**220**) were isolated from the stems and leaves of *Schisandra wilsoniana*, a climbing plant distributed in the Yunnan province of China. All three compounds showed weak anti-HIV-1 activity, with EC_{50} values of 38.3, 99.1, and 118.6 μM in an *in vitro* antiviral assay.[230]



Lancifodilactone H (**221**), a trinorcycloartane triterpenoid with a biosynthetically modified seven-membered lactone ring, and lancifoic acid A (**222**), a new A ring-secocycloartane triterpenoid, were isolated from the stems and leaves of *Schisandra lancifolia*. They exhibited moderate anti-HIV activity, with EC_{50} values of 37.4 and 33.2 μM, respectively.[231]

The genus *Kadsura* belongs to the family Schisandraceae. In an investigation of *Kadsura heteroclita*, a new nortriterpenoid, long-ipedlactone J (**223**), was isolated. When tested in HIV-1_{IIIB} infected C8166 cells, **223** showed a moderate anti-HIV EC_{50} of 7.1 μM.[232]

Four new lanostane triterpenes, colossolactones V, VI, VII,and VIII (**224**–**227**), were isolated from the fruiting bodies of the Vietnamese mushroom *Ganoderma colossum*.[233] With seco A- and E-rings, **224** and **225** differ structurally from previous isolated colossolactones, which have a seven-membered lactone A-ring and six-membered lactone E-ring. Compound **226** has a lactone E-ring, but seco A-ring, while compound **227** has both A- and E-lactone rings. These three new triterpenoids, together with three previously isolated

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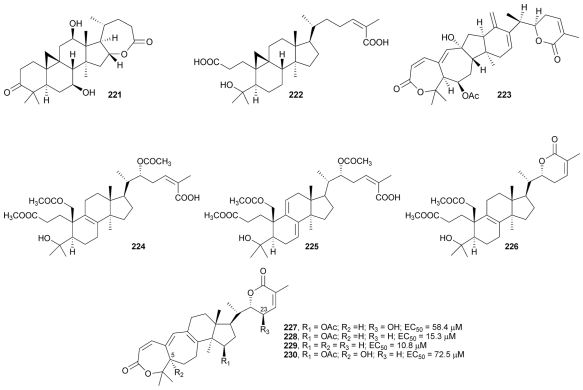
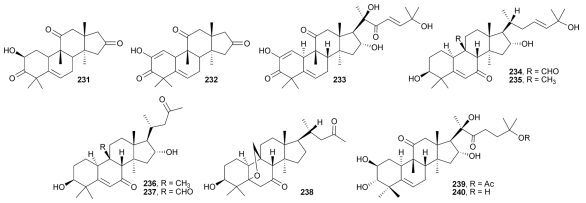
compounds, collosolactone E (**228**), schisanlactone A (**229**), and colossolactone G (**230**), were tested against HIV-1 protease. Compounds **224, 226, 228**, and **229** showed anti-protease activity, with EC_{50} values of 14.6, 24.7, 15.3, and 10.8 μM, respectively, while **225, 227**, and **230** were inactive.[233]



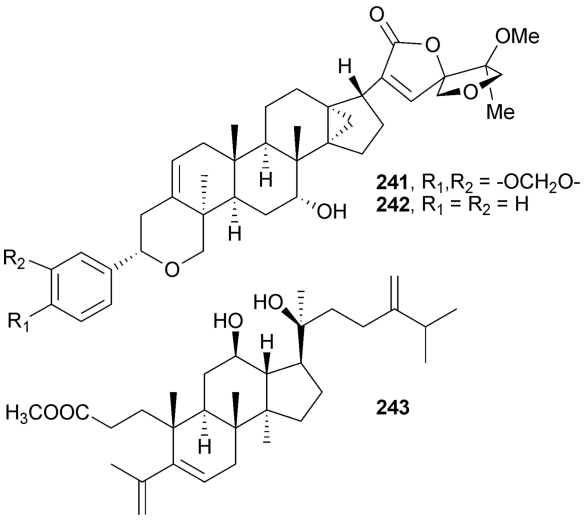
The presence of a hydroxy group at C-23 (R_3) or C-5 (R_2) in the tested compounds reduced the activity (*i.e.*, **227** *vs.* **228** and **230** *vs.* **228**), suggesting that the hydrophobicity of the triterpene skeleton is important to the anti-HIV-1 protease inhibition activity. For the A-ring seco compounds, **224** (with a single double bond at C-8–C-9) exhibited higher activity than the related **225** with two double bonds at C-7–C-8 and C-9–C-11. The unsaturation pattern would alter the three-dimensional structures and, consequently, the spatial arrangement of pharmacophores in the compounds, which have a significant influence on activity. On the other hand, the presence of the seco or lactone A- and/or E-ring did not significantly influence the anti-HIV protease activity of the analogues.

Two unusual octanorcucurbitacins, endecaphyllacins A (**231**) and B (**232**), were isolated from the tubers of *Hemsleya endecaphylla*.[234] These two compounds, together with three known cucurbitane analogues including **99, 100**, and cucurbitacin I (**233**), were evaluated for their ability to prevent the cytopathic effects of HIV-1 in C8166 cells. Although compounds **231** and **232** showed only moderate anti-HIV activity (EC_{50}: 88.27 and 33.70 μM), **99, 100**, and **233** showed significant potency (EC_{50}: 0.16, 0.23, and 1.36 μM, respectively) in this assay.[234] The high activity of **99, 100**, and **233** may be due to the presence of the C-17 functional side chain. However, because **99** is the first reported common cucurbitane analogue with potent antiviral activity, repeated evaluation may be necessary to confirm the compound's potency. Kuguacins A–E (**234**–**238**) were isolated from roots of *Momordica charantia*.[235] They also belong to the cucurbitacin family. Compounds **236** and **238** displayed moderate anti-HIV-1 activity (EC_{50}: 19.7 and 59.6 μM; TI: 23.68 and 7.81, respectively). Although compounds **234** and **235** showed moderate antiviral activity with EC_{50} values of 22.8 and 24.9 μM, they were also cytotoxic, resulting in lower TI values of 7.01 and 3.09, respectively. The cucurbitacin analogues hemslecins A and B (**239** and **240**) were discovered as antibacterial drugs from *Hemsleya jinfushanensis* some time ago. They have recently been shown to have anti-HIV-1 activity, with EC_{50} values of 4.0–36.3 μM and TI values of >20 in different assay systems.[236] Further mechanism of action study revealed that they can block the transmission of virus through cell-to-cell fusion, but cannot inhibit the activities of HIV-1 RT, PR, NCp7 zinc ejection, or viral replication in chronically infected H9 lymphocytes.[236] Thus, it is likely that **239** and **240** function as HIV-1 entry inhibitors.



3.4 The dammarane and euphane groups

Compounds **116–118**, together with acutissimatriterpenes C (**241**) and D (**242**), were isolated from *Phyllanthus acutissima.*[150] The anti-HIV-1 activity of the newly discovered compounds was tested by using a cell-based antiviral replication assay and HIV-1 reverse transcriptase (RT) assay. Compounds **118** and **242** exhibited moderate antiviral replication activity, with EC_50 values of <5.8 and 8.3 μM, respectively, while **116, 117**, and **241** showed weak anti-HIV activity (106.1–130.9 μM). Interestingly, **116** and **117** inhibited the RT by 55.5% and 65.9% at the tested concentration (^300 μM), while **241** and **242** showed only 11.0% and 37.8% inhibition against RT. In comparison, compound **242** did not inhibit RT, suggesting that RT may not be the compound's target.[150] The anti-HIV-1 activity and mechanism of action of C-31-secodammarane triterpenoids isolated from *Alnus firma* were reviewed by Yu *et al.*[237] Among them, alnustic acid methyl ester (**243**) exhibited anti-HIV protease activity, with an EC_{50} value of 15.8 μM. Other similar compounds showed no effect against RT or protease.



3.5 Other triterpenes

Two hopane triterpenes, dryopteric acids A (**244**) and B (**245**), were isolated from the rhizome of *Dryopteris crassirhizoma* (Aspidiaceae), and tested against recombinant HIV-1 protease (PR). Both compounds exhibited moderate anti-HIV protease activity, with EC_{50} values of 26.5 and 44.5 μM, respectively. In comparison, ursolic acid (**46**) has an EC_{50} of 8.9 μM. Acetylation of the C-2 hydroxy group of **244** and **245** yielded compounds **246** and **247**, which showed enhanced anti-protease activity compared with the parent compounds.[238] These results suggested that the carboxylic group at the C-4β (C-24) position and acetyl group at the C-2 position could play key roles in the inhibition of HIV-1 protease in this hopane series of triterpene acids.[238]

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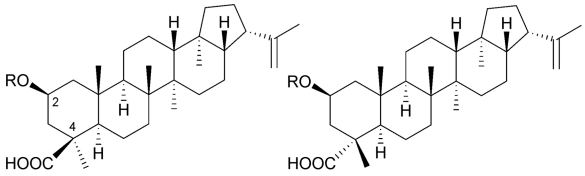

244, R = H; IC_{50}: 26.5 μM
246, R = Ac; IC_{50}: 1.7 μM
245, R = H; IC_{50}: 44.5 μM
247, R = Ac; IC_{50}: 10.8 μM

4 Conclusion

Triterpenoids are an important group for biologically active natural compounds, particularly with approximately 300 new triterpenoids identified each year. Since 1985, Connolly and Hill have regularly reviewed the scientific literature dealing with triterpenoid characterization from natural resources.[239–256] Although numerous triterpenoids possessing various scaffolds have been reported, only a small portion of them were explored systematically for their pharmacological activities. Of those so explored, most showed only marginal potency in preliminary screening. However, this fact does not mean that they should be eliminated from further investigation. For instance, while betu-linic acid (**1**) exhibited only moderate anti-HIV activity, with an EC_{50} of 1.4 μM, modification of **1** furnished the clinical trial agent, bevirimat (**161**), soon to be a phase III anti-HIV drug. Another example is CDDO (**63**), a promising anticancer candidate in phase I clinical trials, which was derived from oleanolic acid (**62**), a weak antitumor compound. Generally speaking, bioactivity-directed fractionation and isolation (BDFI) is a major approach for new lead generation, which is then followed by lead optimization based on rational drug design, synthesis, and bioevaluation, as well as structure–activity relationship (SAR) and quantitative-SAR (QSAR) studies. Selection of a preclinical candidate also involves rapid, efficient assays to gather absorption, distribution, metabolism, excretion, and toxicity (ADMET) data, permitting an effective evaluation of drug candidates in the early stages of the drug discovery process. Although there are still some concerns, especially regarding structure complexity and non-specific pharmacological effects of naturally occurring bioactive triterpenoids, their diversity and uniqueness make them worthy of further pursuit for the discovery of new drugs.

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Biographies

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Susan L: Morris-Natschke received her B.S. in chemistry from the University of Maryland at College Park (1975) and her Ph.D. in organic chemistry from the University of North Carolina at Chapel Hill (1982). She is currently Research Professor in the Division of Medicinal Chemistry and Natural Products, in the .UNC Eshelman School of Pharmacy, where she has been on the faculty since 1983. Her interests include scientific writing/editing, as well as the synthesis and structure–activity relationships of bioactive natural products.

Kuo-Hsiung Lee received his B.S. in pharmacy at Kaohsiung Medical University, Taiwan (1961), his M.S. in pharmaceutical chemistry at Kyoto University, Japan (1965), and his Ph.D. in medicinal chemistry at the University of Minnesota, Minneapolis (1968). Since 1970, he has been on the faculty of the UNC Eshelman School of Pharmacy, and is now Kenan Professor of Medicinal Chemistry and Director of the Natural Products Research Laboratories. He has published over 640 research articles, been granted over 70 patents, and received numerous awards, including most recently the Norman R. Farnsworth Research Achievement Award, American Society of Pharmacognosy (2009).

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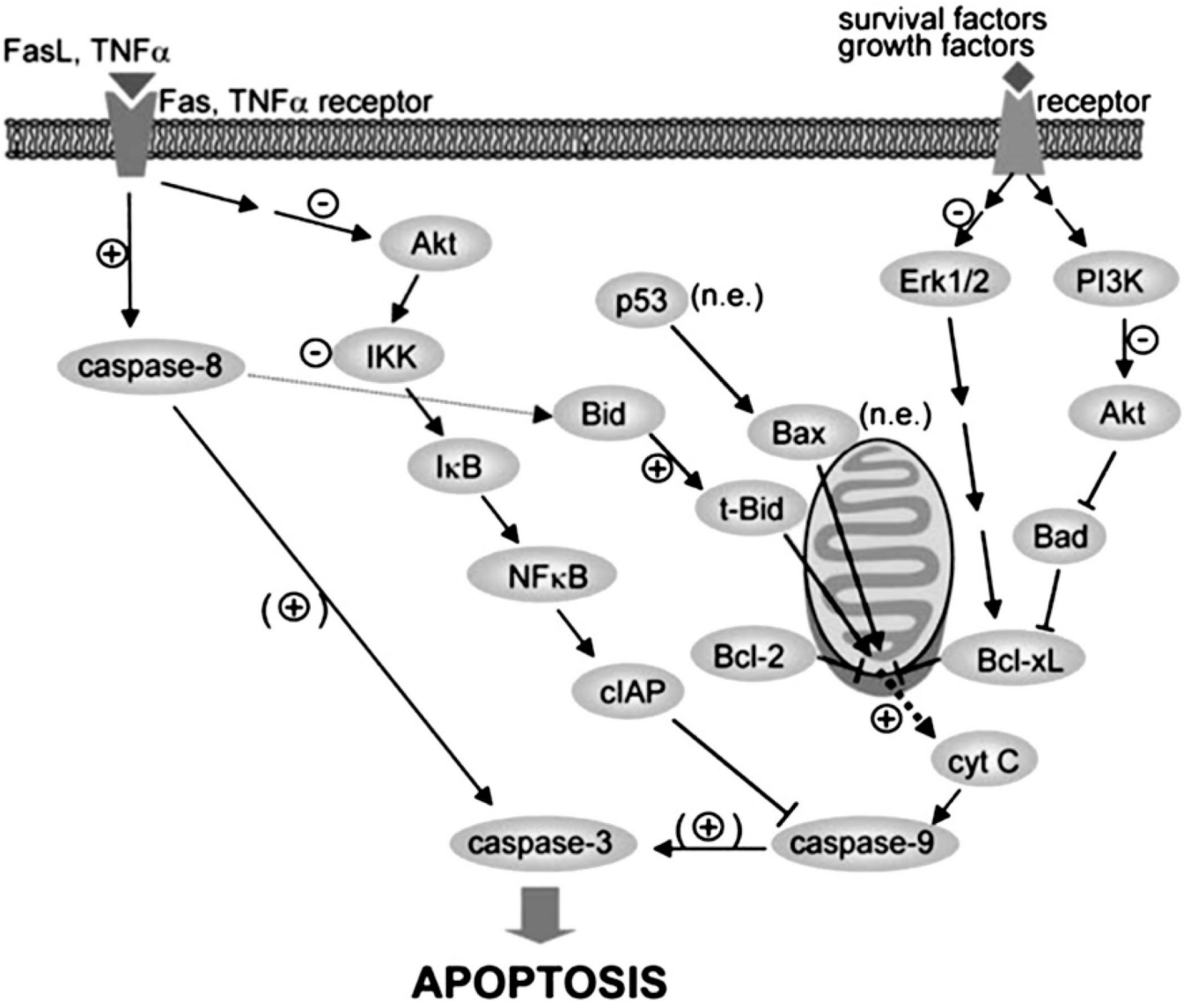

Fig. 1.

Simplified apoptotic signaling scheme and modulation by AKBA (from ref. 83): (+) positive or upregulatory effects of AKBA; (−) negative or inhibitory effects. IKK is the only target for which a direct inhibition by AKBA has been postulated. n.e.: no effect.

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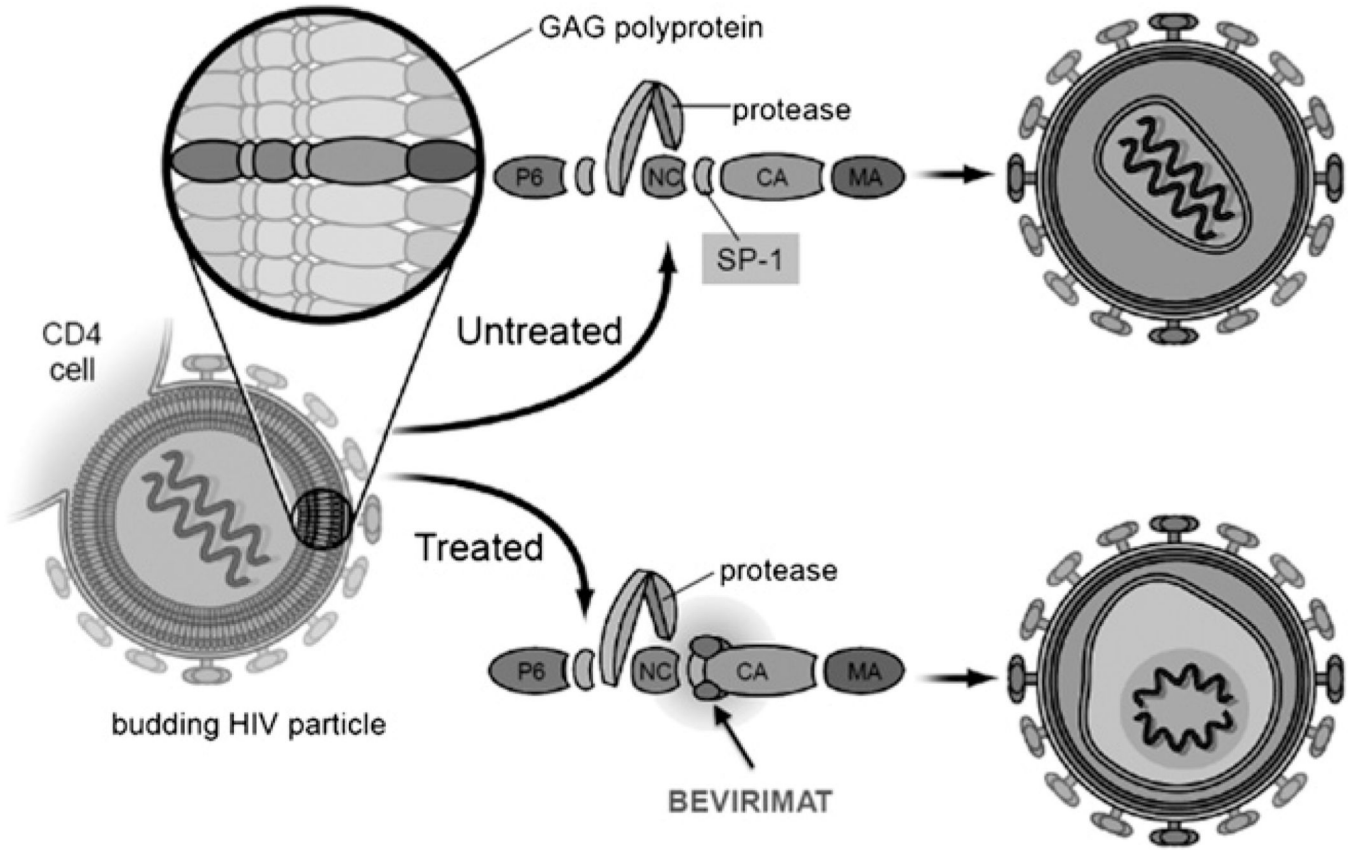

Fig. 2.

Bevirimat (**161**) targets Gag at the CA-SP1 cleavage site to interfere with the processing of p25 into mature p24, resulting in the production of morphologically defective, non-infectious viral particles. (Panacos, XVII international HIV drug resistance workshop, Spain, 2008).

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Table 1

Sources of betulinic acid (**1**)

Part used	Plant origin
Roots	*Ainsliaea acerifolia*[26]
	Helicteres angustifolia[27]
	Mimosa pudica[28]
Root bark	*Harungana madagascariensis*[29]
	Ziziphus cambodiana[30]
Bark	*Alnus hirsuta*[31]
	Platanus orientalis[32]
Stems	*Hydnocarpus hainanensis*[33]
Stem bark	*Barringtonia racemosa*[34]
	Dichapetalum gelonioides[35]
	Diospyros crassiflora[36]
	Diospyros decandra[37]
	Fagara tessmannii[38]
	Psorospermum glaberrimum[39]
	Terminalia superba[40]
Heartwood	*Diospyros paniculata*[41]
Aerial parts	*Gouania ulmifolia*[42]
	Lippia dulcis[43]
	Ocimum basilicum[44]
	Perovskia abrotanoides[45]
	Scoparia dulcis[46]
Stems and leaves	*Jasminum lanceolarium*[47]
Leaves	*Lycopus lucidus*[48]
	Salacia chinensis[49]
	Ugni molinae[50]
Leaves and twigs	*Clematoclethra actinidioides*[51]
	Cratoxylum arborescens[52]
Hulls	*Prunus dulcis*[12]
Whole plant	*Cunila spicata*[53]
	Dracocephalum forrestii[54]
	D. komarovi[55]
	Hyptis fasciculata[53]

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Table 2

Cytotoxicity of **106**–**108** against MCF, SK-MEL-2, and B16 cancer cell lines.[145]

	IC_{50} (μm)		
Cell line	**106**	**107**	**108**
MCF-7	0.62	2.69	1.86
SK-MEL-2	1.82	2.19	0.19
B16	7.62	6.66	0.37

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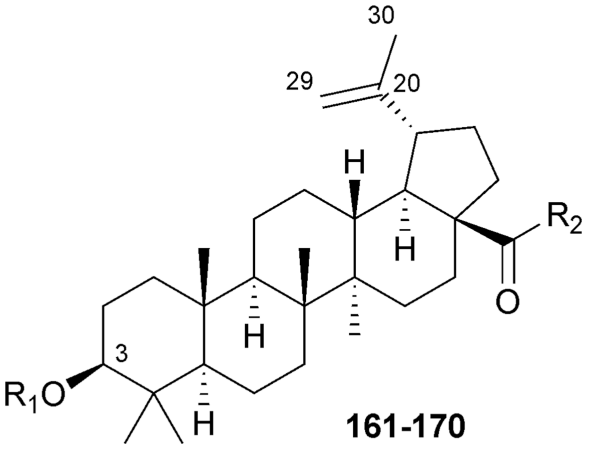
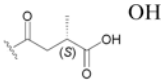
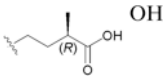
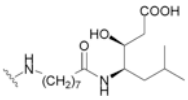
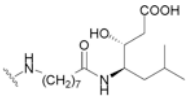
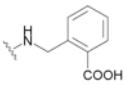
Table 3

Structures and anti-HIV activity of C-3- and/or C-28-modified betulinic acid (**1**) derivatives **161**–**170**[a]



No.	R_1	R_2	IC_{50} (μM)
161 (Bevirimat)	DSB	OH	0.00035[196] 0.0013[197] 0.011[205]
162		OH	0.0087[197]
163		OH	0.12[197]
9	H		0.053[202]
164	H		0.05–2.00[199]
165	H	-NH-$(CH_2)_7$-$NHCOCH_3$	0.047[202]
166	DSB	-NH-$(CH_2)_7$-$NHCOCH_3$	0.0026[202]
167	DSB		0.007[205]
168	DSB		0.006[205]
169	DSB		0.006[206]

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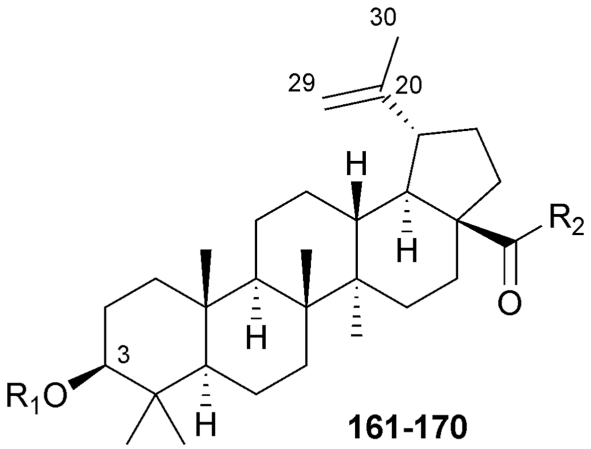
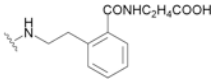


No.	R_1	R_2	IC_{50} (μM)
170	DSB		0.003[206]

[a]DSB: 3′,3′-dimethylsuccinyl.

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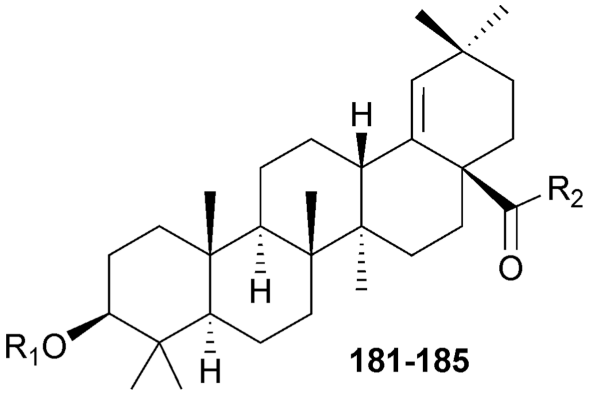
Table 4

Structures and anti-HIV activity of moronic acid (**181**) and its C-3- and C-28- modified derivatives **182**–**185**



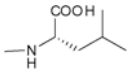
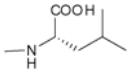
No.	R_1	R_2	EC_{50} (μM)
181	H	OH	0.220[214]
182	DSB		0.017[211]
183	DSB		0.016[211]
184	DSB	$-NH(CH_2)_{10}COOH$	0.007[211]
185	DSB	$-NH(CH_2)_7NHCOCH_3$	0.055[210]

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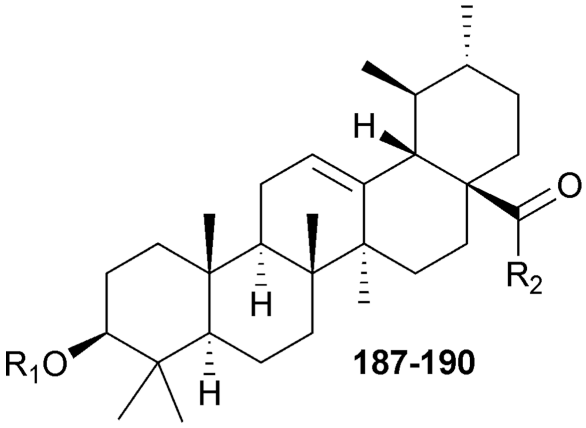
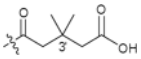
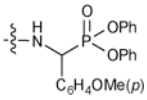
Table 5

Structures and anti-HIV activity of C-3- and C-28-modified ursolic acid derivatives (**187**–**190**)



No.	R_1	R_2	EC_{50} (μM)
187	DSB	$-NH(CH_2)_7NHCOCH_3$	0.23[210]
188	DSB	OH	0.08[211]
189		OH	0.68[211]
190	Ac		0.1 (EC_{20})[217]